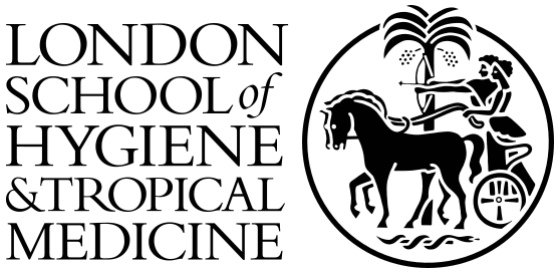

LOW BIRTH WEIGHT AS A RISK FACTOR FOR UNDERVACCINATION IN GHANA; EVIDENCE FROM A POPULATION-BASED COHORT

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LIST OF ABBREVIATIONS

AGA	Appropriate for gestational age
ANC	Antenatal care
BCG	Bacille *Calmette-Guérin*
CBSVs	Community Based Surveillance Volunteers
CHPS	Community Health Planning System
CI	Confidence Interval
DHS	Demographic and Health Survey
DTP	Diphtheria Tetanus Pertussis
EPI	Expanded Programme on Immunisation
GA	Gestational age
GBS	Group B streptococcus
GHS	Ghana Health Service
HB	Hepatitis B
HDSS	Health and Demographic Surveillance System
Hib	*Haemophilus influenzae* type b
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IDB	Inter-database
IQR	Interquartile range
IRR	Incidence rate ratio
KHRC	Kintampo Health Research Centre
KG	Kilogram
LBW	Low birth weight
LMICs	Low and middle income countries
LMP	Last menstrual period
LSHTM	London School of Hygiene & Tropical Medicine
MCV	Measles containing vaccine
MICS	Multiple indicator cluster survey
MLBW	Moderately low birth weight
MMR	Measles mumps rubella
NLBW	Non-low birth weight
NMR	Neonatal mortality rate
OPV	Oral polio vaccine
OR	Odds ratio
Penta	Pentavalent vaccine (Diphtheria, Tetanus, Pertussis, *Haemophilus influenza* type b, Hepatitis B.)
R&C	Range and consistency
RCT	Randomised controlled trial
RR	Rate ratio or risk ratio
SIAs	Supplementary Immunisation Activities
SSA	Sub-Saharan Africa
SES	Socio-economic status
SFI	Serious febrile illness
SGA	Small for gestational age
TB	Tuberculosis
TBAs	Traditional Birth Attendants
TR	Time ratio
UNICEF	United Nations Children's Emergency Fund
VA	Verbal autopsy
VLBW	Very low birth weight
VPD	Vaccine preventable disease
WHO	World Health Organisation

ABSTRACT

In this thesis I analysed population-based data on 22955 infants enrolled in a neonatal vitamin A supplementation trial in rural Ghana to investigate whether low birth weight (LBW: born weighing <2.50kg) was a risk factor for under-vaccination. I also investigated whether under-vaccination among LBW infants was occurring within a broader context of poorer health outcomes such as increased mortality, illness and health facility admissions and lower care-seeking. I additionally investigated how using routine contacts with health services (opportunities for vaccination) could be used to improve their vaccination.

Compared to non-LBW (NLBW) infants, LBW infants were less likely to be vaccinated in both the neonatal and postneonatal period. The smaller the baby at delivery the less likely they were to be vaccinated (p-trend <0.0001). By the end of the neonatal period, moderately LBW (MLBW) infants (1.50-1.99kg) were 1.6 times (adjusted odds ratio (aOR)=1.64; 95%CI:1.30-2.08), and very LBW (VLBW) infants (<1.50kg) were 2.4 times (aOR=2.42; 95%CI:1.50-3.88) more likely to be BCG unvaccinated. In the postneonatal period, VLBW infants had an almost 40% lower DTP1 vaccination rate at age 10 weeks (adjusted rate ratio (aRR)=0.58; 95%CI:0.43-0.77) and 18 weeks (aRR=0.63; 95%CI:0.50-0.80). MLBW infants had vaccination rates approximately 25% lower at these time points. Similar results were observed for DTP3.

LBW infants had much higher mortality rates in infancy compared to NLBW infants. Infants weighing 2.00-2.50kg were >2 times (adjusted hazard ratio (aHR)=2.13; 95%CI:1.76-2.59); MLBW infants were >8 times (aHR=8.21; 95%CI:6.26-10.76), and VLBW infants were >25 times (aHR=25.38; 95%CI:18.36-35.10) more likely to die. The trend of higher mortality with lower birth weight was seen in each of the neonatal, early and late infant periods, but the magnitude of the association declined over time. There was also some evidence that LBW infants had increased illness rates in the neonatal period, and in each of the neonatal and early infant periods. An absence of care seeking was found for MLBW infants in the first year of life (aOR=1.46; 95%CI:1.18-1.81), and in each of the neonatal (aOR=3.30; 95%CI:1.98-5.48) and early infant periods (aOR=1.74; 95%CI:1.26-2.39) respectively. No association was found in the late infant period (p-interaction=0.0002).

Among all infants (NLBW and LBW) with opportunities for vaccination, most opportunities were missed. There was no association between birth weight and uptake of opportunities.

In conclusion LBW infants are under-served by vaccination in Ghana. Given their poorer health outcomes, efforts to improve their access to care services, including vaccination are warranted. Further research into the barriers and facilitators of vaccination of LBW infants is warranted, including qualitative research targeting care givers and vaccine providers.

BACKGROUND AND METHODS

CHAPTER 1: BACKGROUND

Preamble

In this chapter, I introduce the topics covered by this PhD, and I present relevant background data. Specifically, I describe i) the important role of vaccination in reducing the burden of infectious disease-related child mortality in Sub-Saharan Africa, ii) current global policy on the importance of identifying groups that are under-served by vaccination, and iii) why low birth weight infants may be one such under-served group. I outline the rationale for the research, and I define the aims and objectives of the PhD. Finally, I describe the structure of the thesis.

1.1. INFECTIOUS DISEASES AND CHILD MORTALITY IN SUB-SAHARAN AFRICA

In 2015 almost 50% of all deaths worldwide in children aged less than five years (an estimated 3 million deaths) occurred in Sub-Saharan Africa (SSA)[1]. A large burden of these deaths occurred in the postneonatal period (4-51 completed weeks of age). In 29 countries of SSA, at least 60% of under-five deaths were postneonatal deaths[2]. In 2015, infectious diseases were responsible for approximately half of all deaths among under-fives[2]. Pneumonia and diarrhoea were estimated to be responsible for 18% and 9% of all under-five deaths respectively[2].

1.2. THE ROLE OF VACCINATION IN REDUCING INFECTIOUS-DISEASE RELATED CHILD MORTALITY

Vaccines have been developed against a number of infectious diseases and the World Health Organisation (WHO) estimates that up to 2.5 million deaths among children less than five years are prevented each year by vaccination against diphtheria, tetanus, pertussis (DTP) and measles[3,4]. Effective implementation of vaccination programmes can have dramatic impacts. For instance, the annual measles mortality rate in under-fives declined by almost 15% between 2000 and 2010, almost four times the overall rate of decline in under-five mortality[5]. Nevertheless, in 2013 one in every five children was not fully vaccinated by 52 weeks of age, and almost three out of every 10 deaths among children aged one to 59 months were estimated to be due to vaccine preventable diseases

(VPDs)[6]. Due to lower vaccine coverage rates in the region, SSA now accounts for a disproportionate burden of vaccine preventable diseases (VPDs). Data from 2008 (to the best of my knowledge, the most recently available data), reported that globally 46% of all deaths due to VPDs occurred in SSA[7].

1.3. RECOMMENDED SCHEDULE FOR ROUTINE VACCINATION

WHO makes specific recommendations for the minimum age at initiation and staging of routine childhood vaccines (**Table 1.1)**[8,9].

Table 1.1: Summary of WHO recommendations for the administration of selected vaccines included in the routine childhood vaccination schedule[8,9].

Antigen	Doses in Primary Series	Age of 1st dose	Interval between Doses
Bacille Calmette-Guerin (BCG)	1	Neonatal period / as soon as possible after birth	-
Oral Polio Vaccine (OPV)[1]	3	6 weeks	4 weeks (minimum) (with DTP)
Diphtheria Tetanus Pertussis (DTP)[2]	3	6 weeks (min)	4 weeks (minimum) – 8 weeks
Haemophilus influenza type b (Hib)	3	6 weeks (min) with DTP1, 24 months (max)	4 weeks (minimum) (with DTP2 & 3)
Hepatitis B (HB)[3]	3 – 4	At birth (<24 hrs)	4 weeks (minimum) (with DTP2 & 3)
Measles containing vaccine (MCV)[4]	2	9 or 12 months	4 weeks (minimum)
Yellow Fever	1	9 – 12 months with measles	-
Pneumococcal (conjugate)	4	6 weeks (min) with DTP1	4 weeks (minimum) (with DTP2 & 3)
Rotavirus	2 (Rotarix) 3 (Rota Teq)	6 weeks (min) with DTP1, 15 weeks (max)	Rotarix - 4 weeks (minimum) (with DTP2) no later than 32 weeks of age Rota Teq - 4 weeks (minimum) – 10 weeks with DTP2

1 In countries with a high risk of importation or transmission of polio, an additional OPV dose should be given as soon as possible after birth
2. Last dose of primary series to be completed by 6 months. A booster dose is recommended at between 1 and 6 years of age; at least 6 months after last primary dose
3. Preterm low birth weight (LBW) infants may not respond well to HBV vaccination at birth. Doses given to infants weighing <2000g do not count towards primary series. By 1 month of age, preterm infants are likely to respond adequately, regardless of gestational age or weight at birth.
4. First dose should be administered at a minimum age of six months

Recommended schedules are informed by the underlying epidemiology of the target organism in the target population and the timing that will generate the maximum immune response with the minimum risk of adverse events[10,11]. Deviation from the schedule may result in a sub-optimal immune response at the individual level and at a population level may reduce the effectiveness of the overall vaccination programme[10,11].

1.4. EVALUATION OF ROUTINE VACCINE PROGRAMMES: CURRENT APPROACHES AND GAPS IN THE DATA

Routine monitoring of vaccination programmes is essential to evaluate programme performance and effectiveness, to inform modifications to the programme and to guide strategies for the containment of VPDs[12]. Vaccine uptake, defined as the proportion of the target population that has been vaccinated, is a key indicator in vaccination programme evaluation[12].

1.4.1. Methods of assessing vaccine uptake

WHO and the United Nations Children's Emergency Fund (UNICEF) generate estimates of uptake for each dose of each vaccine in the recommended schedule using a combination of administrative data (routine reports of the number of vaccinations given by service providers such as health centres, vaccination teams and private physicians over a given time) and data from household surveys[12,13]. Both data sources are subject to a number of well-described limitations[12,13]. For instance, the validity of administrative data is limited by incomplete reporting and inaccurate denominator data, leading sometimes to reported uptake rates in excess of one hundred percent. Populations likely to be missed in household surveys may also be missed by vaccination teams, and this can lead to overestimates of coverage[14]. Children who die may be under-represented in these surveys, and they may be less likely to be vaccinated, consequently selection bias may be a substantial problem in populations with high infant mortality[14]. For all vaccines except BCG (which uses live births as a denominator), the reported estimates refer to uptake at 52 weeks of age and the denominator only includes children who live to 52 weeks of age[12]. Estimates refer to all vaccinations given, regardless of whether they adhere to recommendations on the timing and staging of vaccination[12].

1.4.2. Gaps in the data

Although many countries report high uptake rates for individual vaccines at 1 year of age, and although overall their vaccination programmes perform very well, almost 19 million children still do not receive all of their vaccines every year[15]. Considerable disparities in coverage persist, both between and within countries. Studies of the timely delivery of vaccines report that whereas uptake of routinely scheduled vaccines is generally high, a substantial proportion of children are vaccinated late[16-20]. An analysis of demographic and health survey (DHS) data for 217706 infants from 45 countries reported median vaccination delays of 2.3 weeks (interquartile range (IQR):1.4-4.6) for BCG, 2.4 weeks (1.2-3.3) for DTP1,

6.2 weeks (3.5-8.5) for DTP3 and 2.7 weeks (1.7-3.1) for MCV[16]. An analysis of 1403 infants recruited in a community-based cluster survey in southern Tanzania reported that 33% of infants were delayed in their vaccination with BCG (vaccinated >1 month after the vaccine due date), as were 34% for DTP1, 69% for DTP3 and 46% for first dose MCV[21]. An analysis of a population-based cohort in Ghana reported median delays of 2 to 4 weeks for all vaccines except birth oral polio vaccine (OPV), which had a median delay of 5 days[22].

Timely administration of vaccines is important. For infections that are most prevalent in the first few months of life, such as those caused by pertussis[23], *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae*[19,24], delayed vaccination may prolong the risk of infection and may reduce the effectiveness of the vaccination programme, even if the uptake at 52 weeks of age is high[16,19]. Unfortunately, data on the timely administration of vaccines are not currently included as an indicator in routine programme evaluations and so the increased time at risk for contracting a VPD among those who are delayed in being vaccinated is not accounted for. Given this, there is increasing interest in monitoring the timeliness of vaccination and in characterising those at greatest risk of vaccination delay[25].

Vaccine uptake estimates are reported for the total population. No estimates on uptake among those most at risk of under-vaccination, for instance among low birth weight (LBW) infants are routinely available. This is further explained in **Section 1.5**.

1.4.3. Assessing the timely delivery of vaccines

There are a number of different approaches to the assessment of timeliness (**Table 1.2**). These include 1) estimating time to vaccination using survival analysis techniques such as Kaplan Meier curves or Cox regression[16,17,19,22,26,27,30,31,35,36,42]; 2) estimating the number of additional days a child was under-vaccinated[37] or at risk of a VPD due to delayed administration of each vaccine[41]; 3) estimating the proportions delayed in the receipt of their vaccinations (using predefined cut-offs for delayed vaccination)[20,21,25,30,34,35,39] and 4) estimating age-specific up-to-date vaccination rates[28,29,32,33,38,40]. Person-time analysis techniques, such as Cox and Poisson regression, provide the most accurate measure of timely delivery of vaccines as they account for the early censoring of individuals due to death or loss to follow up and allow these individuals to be included in the analyses.

Table 1.2: Summary of outcomes and analytical methods in published studies that assessed timely vaccination

Citation, Country	Outcome Measures	Methods
Gram et al, 2014 [22] Ghana	Received vaccination within first year of life Vaccination within 1, 2, 4 and 6 weeks of due date Received all vaccinations appropriate for a particular age Median time to vaccination in weeks	Kaplan Meier Cox regression
Le Polain de Waroux et al, 2013 [21] Tanzania	Delayed vaccination defined as vaccination at > 1month after the recommended age of vaccination	Kaplan Meier Log binomial regression
Babirye et al, 2012 [26] Uganda	Time to vaccination for BCG (birth to 8 weeks), Polio 0 (birth – 4 weeks), Polio1 / DTP1 (4-2 months), Polio2 / DTP2 (8 weeks – 4 months), Polio3 / DTP3 (12-6 months) & measles (38 weeks to 12 months)	Kaplan Meier Cox regression
Akmatov & Mikolajczyk 2011 [17] 31 LMICs*	Delayed vaccination – vaccination > 1month after recommended age Up-to-date vaccination for children aged 12-59 months (BCG, DTP & Polio) and 18-59 months (measles). Age-specific vaccination coverage.	Kaplan Meier Multilevel logistic regression
Fadnes, 2011 [27] South Africa	Timely vaccination (vaccination within recommended time-periods (birth to 8 weeks for BCG, birth to 4 weeks for birth OPV, 4 weeks to 2 months for DTP1, 8 weeks to 4 months for DTP2, 12 weeks to 6 months for DTP3, 38 weeks to 12 months for measles))	Kaplan Meier Cox regression
Mutua et al, 2011 [28] Kenya	Full vaccination at 24 months of age Up-to-date vaccination (receipt of BCG, OPV 1-3, DTP 1-3 & measles) at 3 and 12 months of age	Descriptive analysis Multivariable logistic regression
Moisi et al, 2010 [19] Kenya	Vaccine uptake at 2, 4, 6, 10, 14, 18 & 22 weeks of age, & at 9, 10, 11, 12 months of age Time to vaccination Median & IQR for age at vaccination.	Kaplan Meier Log-rank tests. Cox regression
Sadoh & Eregie, 2009 [20] Nigeria	% of children vaccinated a) too early (before recommended age), b) on time (within 2 weeks of due date), c) acceptably late (2-4 weeks after due date) and d) delayed (>4 weeks after due date) Mean & median age at vaccination Mean difference between age at vaccination & recommended ages	Descriptive analysis
Clarke & Sanderson, 2009 [16] 45 LMICs	Age-specific coverage rates Median, quartiles and IQRs for delays in days for each vaccine Uptake within the first year of life Uptake within 1, 2, 4 and 6 weeks of the due date	Kaplan Meier Cox regression

Continued…..

Table 1.2 continued

Citation, Country	Outcome Measures	Methods
Corsi et al, 2009 [29] India	Up-to-date & age-appropriate vaccination Infants were age-appropriately vaccinated if they had received BCG by 1 month of age, BCG & 1 dose of OPV/DTP by 2 months, BCG & 2 doses of OPV / DTP by 3 months, BCG & 3 doses of OPV/DTP by 4 to 8 months and BCG, 3 doses of OPV / DTP & 1 dose of measles by 9 months	Descriptive analysis
Akmatov et al, 2008[30] Armenia, Kazakhstan, Kyrgyzstan, Uzbekistan	% of children aged 12-35 months and 12-59 months who were up-to-date with DTP vaccination. % aged >18months up-to-date with measles. Time to vaccination Delayed vaccination (vaccination 1 month after the recommended age).	Descriptive analysis of % up-to-date Kaplan Meier Multinomial logistic regression
Santibanez et al, 2006. [31] USA	% of children who received 3 or more doses of DTP by 7 months of age & 1 or more dose of MMR by 19 months of age. Cumulative vaccination coverage for DTP3, DTP4 & MMR1 by age in months	Chi-square test. Kaplan Meier
Fiks et al, 2006 [32] USA	Up-to-date vaccination at 3, 7, 13 and 24 months. Determinants of delay (defined as not being up-to-date at 24 months)	Calculation of relative risks and attributable risks of delay at 24 months. Logistic regression
Cui & Gofin, 2006[33] China	Up-to-date vaccination in children aged 12-23 months at 3, 8 and 12 months of age	Descriptive analysis Logistic regression
Hull & MacIntyre, 2006 [34] Australia	Age-appropriate vaccination – within 30 days of recommended age % vaccinated on time, acceptably early, 1-6 months delay, > 6 months delay, not vaccinated at 24 months.	Descriptive analysis
Dayan et al, 2006[35] Argentina	% up-to-date and delayed vaccinated at time of interview. Age-specific vaccination coverage Determinants of delayed vaccination. Delayed vaccination defined as not receiving vaccine at > 1 month after the scheduled age. (Excluded invalid vaccination doses)	Kaplan Meier Log-binomial regression analysis
Ndiritu, 2006 [36] Kenya	Median age at vaccination Determinants of time to vaccination	Kaplan Meier Cox regression

Continued…

Table 1.2 continued

Citation, Country	Outcome Measures	Methods
Luman et al, 2005 [37] USA	Cumulative days under-vaccinated during the first 24 months of life for each of six vaccines and all vaccines combined. Under-vaccination defined as vaccination at > 1months after the recommended age. - % of children delayed 0 days, 1- 7 days, 8-31 days, 1-2 months, 3-6 months, 7-12 months & > 12 months. - No. of late vaccines - Risk factors for severe delay in vaccination (defined as under-vaccinated for > 6 months for >= 4 vaccines).	Descriptive analysis Logistic regression
Strine et al, 2003 [38] USA	Completion of 4 dose DTP by 24 months of age On time receipt of DTP4 between 12 and 18 months of age (< 19 months)	Logistic regression
Dombkowski et al, 2002 [25] USA	Months of vaccination delay relative to age-appropriate vaccination standard Up-to-date DTP4, OPV3 and MMR1 and complete 4:3:1 series DTP4 & OPV3 at > =19 months were defined as delayed; MMR at >=16 months.	Mean rates of vaccination delay & chi-square tests of association
Luman et al, 2002[39] USA	Age at receipt of vaccines among children aged 24-35 months % vaccinated on-time (receipt within 1 month of recommended age) % acceptably early (within 4 days before the minimum acceptable age until the routinely recommended age), late (> 1 month after the recommended age but before 24 months of age), unvaccinated by 24 months and too early to be valid (> 4 days before the minimum acceptable age) Determinants of timely vaccination	Descriptive analysis Logistic regression
Langkamp et al, 2001 [40] USA	Age at receipt of each of the first 4 doses of DTP, first 3 doses of polio and first dose of MMR. Comparison of the mean age at receipt of each dose of DTP, polio and MMR for VLBW, MLBW and NLBW. % of children up to date for all vaccinations at 12, 24 and 36 months. Determinants of being up-to-date for all vaccinations at 12, 24 and 36 months	Descriptive analysis Logistic regression
Kahn et al, 1995 [41] Central African Republic	Additional days at risk for measles (age in days at vaccination minus 270 days) Age in months to measles vaccination	Descriptive analysis

** LMICs = Low and middle income countries; VLBW=very LBW (weighs <1.50kg at birth); MLBW = moderate LBW (weighs 1.50-1.99kg at birth)*

Surveys solely investigating uptake at predefined cut-offs to assess timely vaccination are less sensitive, as individuals whose follow-up is censored before that time point are excluded. As the rate of vaccination in infants who die or who are lost-to-follow-up may be different to surviving infants, excluding these infants may lead to over-estimates of the timeliness of delivery.

1.5. IDENTIFYING GROUPS AT RISK OF UNDER-VACCINATION

There have been many studies to investigate the factors associated with non-vaccination and delayed vaccination among children in low and middle income countries (LMICs)[19,28,43-45]. The factors include lower socioeconomic status (SES)[21,28,46,47], being a member of a minority ethnic or religious group [21,28,47], increasing distance to a health facility,[19,21,47] being born at home[28,47], lower maternal education[21,28,46,47] and age[28], child's higher birth order[28,47], increased family size[47], wet season[19,21], female sex[47], positive maternal human immunodeficiency virus (HIV) status[45] and parental knowledge and understanding of vaccination[44,47-49].

Measles vaccine coverage in some countries is 33% lower in rural areas than in urban areas and almost 60% lower among the poorest quintile of the population compared to the richest[4]. Migrant populations and those living in urban slums are also known to have lower vaccine coverage. All these under-vaccinated population groups are likely to suffer from a higher disease burden and so ensuring their access to and uptake of preventative care services such as vaccination is essential to address health inequalities, to maximise the impact of these interventions, and to facilitate economic development. Furthermore engagement of these groups is critical to address disease elimination and eradication targets[4].

Given this, the latest Global Vaccine Action Plan for 2011 to 2020 has specifically advocated for the identification and targeting of groups who are under-served by routine vaccination services[4]. Identifying hard-to-reach groups and groups at risk of under-vaccination, as well as the factors associated with under-vaccination, have all been identified as priority research areas to improve the delivery of vaccines in developing countries[50] .

In countries lacking population-based surveillance systems and robust health information systems it can be difficult to identify those sub-groups of the population who are under-vaccinated. Further work is therefore needed to identify specific risk factors of the under-

vaccinated which will facilitate their easy identification. Low birth weight may be one such risk factor.

1.6: LOW BIRTH WEIGHT INFANTS

LBW infants are born weighing less than 2.50 kilograms (kg) at birth irrespective of gestational age[51,52]. LBW is due either to preterm birth (defined as delivery before 37 weeks of gestation) or restricted foetal (intrauterine) growth[53]. Restricted foetal growth can cause infants to be small for gestational age (SGA) (defined as a sex-specific birth weight below the 10th percentile for gestational age as a reference standard[51,52]).

The risk factors for LBW are well described[53-56], and include low socioeconomic status, primiparity and high parity, low maternal age and co-infection with HIV. Most LBW infants (96%) are born in LMICs, where the prevalence is twice that in high income settings[56].

1.6.1. The relationship between birth weight, gestational age, and size for gestational age

In LMICs, accurate data on gestational age (GA) are frequently lacking and so LBW is commonly used as a proxy for preterm birth[57]. Birth weight does not directly correlate to gestational age, and so direct comparisons are problematic[57]. For instance only about 50% of infants weighing 2.00-2.50kg are preterm[57], and a substantive proportion of non-LBW (NLBW) infants are SGA (21% in South Asia and 16% in Africa)[52]. Nonetheless, a birth weight of less than 1.50kg (very low birth weight, VLBW) is considered a specific and sensitive marker for preterm delivery[58,59]. In SSA in 2010, about 24% of all infants were estimated to be term and SGA, about 10% were pre-term and appropriate for gestational age (AGA) and approximately 2% were both preterm and SGA[51]. This is compared to an estimated prevalence of LBW of 14%[51]. Not all infants that are SGA or pre-term are LBW.

1.6.2. Population level assessment of LBW

Estimates of LBW are subject to a number of well-documented biases[56,60-62] associated with 1) the large proportion of infants missing birth weight data and 2) the measurement, recording and recall of birth weight data.

In LMICs almost 50% of infants are not weighed at birth[60]. Those infants who are weighed are more likely to be born to wealthier women with higher levels of educational attainment who deliver in facilities and who are less likely to deliver a LBW infant[60,61,63]. Furthermore, in

surveys, written records of birth weight may be less available for infants who die, as it is common practice for parents to discard the child health records of deceased infants. This may result in an under-ascertainment of birth weight data for LBW infants who are at greater risk of mortality[56]. This may be exacerbated by a general under-reporting of data on infants who die[64]. In order to adjust for these biases, current estimates of the prevalence of low birth weight are now routinely adjusted upwards by an average of 24%[56,60,62].

1.6.3. The consequences of LBW – excess mortality and illness

The association between birth weight and mortality, and illness during infancy in SSA has not been extensively studied. Few studies have generated population-based estimates, especially for the postneonatal period, and for VLBW infants, who, based on data from high-income settings[65,66] are known to be at a particularly increased risk of adverse health outcomes.

I searched Pubmed (up to 13 April 2016) [67] to identify studies on the association between both a) birth weight and b) preterm delivery, and the outcomes mortality, illness and care seeking in SSA. The search terms are detailed in **Annex 1**. I restricted the search to those aged 0-23 months, to humans, and to articles in English, dating from the last 20 years (since 01 January 1996). In addition, I searched the reference list of selected articles. The search yielded 2141 articles, and upon review of the titles, abstracts and reference lists, I identified 18 papers on the association between birth weight and mortality, illness and care seeking (**Table 1.3**). I identified nine studies that generated estimates on mortality[52,68-75], four on mortality and illness[76-79], and five on illness only[80-84].

Many of the studies were limited by small sample sizes[73,78,81,82], or were restricted to specific populations such as HIV exposed infants[74,77,79] or infants born to mothers recruited from antenatal care (ANC)[73,75]. Furthermore, direct comparison between studies was complicated by the use of different exposure variables. Some studies investigated the association with preterm delivery or growth retardation[52,71,78], and others investigated the association with birth weight[70,72,73,75,79].

Table 1.3: Overview of studies from SSA investigating the association between preterm* birth, birth weight and illness and mortality in the first year of life.

Citation	Study population & setting	Exposure	Outcome	Effect estimates (95%CI)
Mortality				
Sania et al, 2014[68]	Prospective cohort study nested within a randomised control trial (RCT). 7225 HIV negative pregnant women enrolled at ANC, Dar es Salaam, Tanzania between 2001 & 2004. Their singleton infants followed up monthly until 1 year of age	Preterm appropriate for gestational age (AGA), term SGA & preterm SGA compared to term AGA (based on LMP) LBW compared to NLBW infants	Adjusted HR[1] for neonatal, postneonatal, & infant mortality.	**Neonatal** Preterm AGA: 2.6 (1.8-3.9) Term SGA: 2.3 (1.6-3.3) Preterm SGA: 15.1 (8.2-27.7) LBW: 7.5 (5.5-10.3) **Postneonatal Mortality** Preterm AGA: 2.5 (1.6-3.9) Term SGA: 0.9 (0.6-1.6) Preterm SGA: 2.6 (0.6-11.9) LBW: 3.2 (1.9-5.3) **Infant Mortality**: Preterm AGA: 2.6 (1.9-3.5) Term SGA: 1.7 (1.3-2.3) Preterm SGA: 10.0 (5.8-17.8) LBW: 5.8 (4.5-7.6)
Debelew et al, 2014[69]	Community based cohort study of 3463 newborn infants in rural Ethiopia in 2012 – 2013.	Maternal report of a) preterm delivery (<37 weeks of gestational age) compared to term & b) small size at birth compared to normal size at birth	Adjusted OR[2] for the determinants of neonatal mortality	a) 2.09 (1.03-4.22) b) 1.95 (1.11-3.42)
Kayode et al, 2014[70]	Secondary analysis of 2003 & 2008 DHS community based household survey data for 6900 women aged 15-49 years Ghana	LBW compared to NLBW infants (based on maternal recall of infant size)	Adjusted OR[2] for the determinants neonatal mortality	2.01 (1.23-3.30)

Continued…

Table 1.3 continued

Citation	Study population & setting	Exposure	Outcome	Effect estimates (95%CI)
Katz et al, 2013[52]	Pooled analysis of data from 20 population-based cohorts from LMICs (>2 million infants) from 1982-2010	Preterm vs term SGA vs AGA LBW vs NLBW (based on mix of ultrasound, clinical assessment and LMP)	Unadjusted RR[3] for neonatal & postneonatal mortality	**African Estimates:** **Neonatal:** SGA: 1.62 (1.14-2.26) Preterm: 7.19 (4.12-12.52) 34-36 wks: 2.74 (1.42-5.26) 32-33 wks: 11.02 (3.93-30.89) <32 wks: 25.79 (15.07-44.14) Term SGA: 2.07 (1.65-2.60) Preterm AGA: 8.02 (4.05-15.91) Preterm SGA: 11.54 (6.76-19.71) **Postneonatal:** SGA: 1.46 (1.09-1.96) Preterm: 1.99 (1.49-2.66) 34-<37 wks: 1.92 (1.62-2.28) 32-<34 wks: 3.01 (1.77-5.14) <32 wks: 3.48 (0.81-14.86) Term SGA: 1.61 (1.40-1.84) Preterm AGA: 1.89 (1.21-2.97) Preterm SGA: 3.65 (2.90-5.48) **Infant:** SGA: 1.52 (1.21-1.91) Preterm: 2.69 (2.28-3.18) 34-<37 wks: 1.75 (1.31-2.34) 32-<34 wks: 2.97 (2.16-4.09) <32 wks: 8.94 (5.98-13.37) Term SGA: 1.68 (1.52-1.86) Preterm AGA: 2.96 (1.89-4.64) Preterm SGA: 4.75 (3.09-7.32)

Continued…

Table 1.3 continued

Citation	Study population & setting	Exposure	Outcome	Effect estimates (95%CI)
Marchant et al, 2012[71]	Meta-analysis of data on 4843 births from 4 cohort studies collected from 1999-2010 1. Kenya: Community based cohort 2. Tanzania Mwanza, Tanzania Korogwe & Uganda: ANC attendees Uganda - home births excluded	1. LBW vs NLBW 2. Preterm vs term 3. SGA vs AGA 4. Preterm & weight for GA strata compared to term AGA	NMR[4] per 1000 live births Unadjusted neonatal mortality OR[2]	**Neonatal mortality OR** **1. LBW:** Overall: 7.64 (4.80-12.15) Tanzania Korogwe: 8.96 (3.88-20.69) Tanzania Mwanza: 17.82 (6.86-46.28) Kenya: 5.49 (2.12-14.16) Uganda: 3.45 (1.27-9.40) **2. Preterm** @ 34-36 wks: 6.25 (3.03-12.87) @<34 wks: 58.74 (28.41-121.45) **3. SGA**: 2.14 (1.33-3.45) **4. Preterm & Weight for GA strata** AGA 34-36wks: 3.18 (0.95-10.71) AGA <34 wks: 74.92 (32.68-171.75) SGA >= 37 wks: 2.23 (1.22-4.10) SGA 34-36 wks: 19.88 (8.33-47.47) SGA <34 wks: 56.97 (11.13-291.73)
Kayode et al, 2012[72]	Secondary analysis of population-based 2003 & 2008 Nigerian DHS data on 28647 infants	LBW vs NLBW	Adjusted OR[2] for under-5 mortality	aOR=1.31 (1.09-1.58)
Bardaji et al, 2011[73]	Cohort study nested within an RCT. 997 infants born to women recruited from ANC at a district hospital in Mozambique, 2003-2005	LBW vs NLBW	Adjusted infant mortality OR[2]	aOR=2.82 (1.27-6.28)
Wei et al, 2004[74]	Cohort study (nested within a micronutrient supplementation RCT) of 823 singleton infants born to HIV infected women recruited from ANC in Dar es Salaam, Tanzania, who delivered in the clinic. Year not stipulated.	LBW vs NLBW	Neonatal mortality adjusted HR[1]	Neonatal: 5.14 (2.32-11.39) Postneonatal: Overall: 1.75 (0.94-3.28) HIV negative/indeterminate: 3.16 (1.36-7.37) Infant: 2.40 (1.45-3.95)

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Table 1.3 continued

Citation	Study population & setting	Exposure	Outcome	Effect estimates (95%CI)
Bloland et al, 1996[75]	Secondary analysis of data on 3724 singleton infants born to women recruited at ANC between 1987-1989 & enrolled in a malaria chemoprophylaxis trial in Malawi	LBW (2.00-2.50kg) VLBW (<2.00kg) Compared to NLBW	Adjusted HR[1] for neonatal, postneonatal & infant mortality	Neonatal: LBW: 2.3 (1.2-4.2) VLBW: 12.7 (7.2-23.0) Postneonatal (only univariable estimates available, as birth weight was excluded from the multivariable model) LBW:1.3 (0.9-1.8) VLBW: 2.4 (1.3-4.4) Infant: LBW: 1.4 (1.0-2.0) VLBW: 5.0 (3.3-7.7)
Illness and mortality				
Doherty et al, 2014[76]	Secondary analysis of 964 HIV unexposed infants enrolled in a community breastfeeding RCT in South Africa in 2006 & 2008. Birth weight recorded from child health card	LBW vs NLBW	Adjusted HR[1] for severe event (hospitalisation or death) in the first 6 months of life	2.4 (1.3-4.3)
Kourtis et al, 2013[77]	Secondary analysis of 2369 HIV exposed uninfected infants enrolled in a breastfeeding antiretroviral & nutrition trial, Malawi. Mothers recruited through ANC. 2004-2010	BW of 2.00-2.50kg vs NLBW	Adjusted HR[1] for neonatal mortality. Unadjusted HR for postneonatal mortality, pneumonia/serious febrile illness (SFI), diarrhoea & malaria (based on clinical diagnosis)	Neonatal mortality: 12.30 (3.55-42.40) Postneonatal mortality: 0.90 (0.28-2.91) Pneumonia/SFI: 1.36 (0.96-1.91) Diarrhoea: 1.05 (0.62-1.80) Malaria: 1.44 (0.69-3.00)

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Table 1.3 continued

Citation	Study population & setting	Exposure	Outcome	Effect estimates (95%CI)
Gladstone et al, 2011[78]	Community based stratified cohort study of 840 infants surviving to 6 weeks of life, nested within an RCT of antibiotic prophylaxis, 2006. All 247 surviving preterm infants in the RCT were included, along with 593 randomly selected term infants. Ultrasound dated GA & self-report of illness	Preterm vs term	Adjusted HR[1] for mortality, visits to health facilities & admissions between 6 weeks and 2 years of life	Mortality: 1.79 (1.09-2.95) No significant differences in reported morbidities or admissions
Kuhn et al, 2005[79]	620 HIV exposed HIV uninfected infants from Lusaka, Zambia, who survived the immediate neonatal period (to day 4 of life); nested within a breastfeeding trial of mothers recruited at ANC, 2002	LBW vs NLBW	Adjusted HR[1] for mortality & hospitalisation by 4 months of age	Mortality: 2.43 (1.05-5.65) No association between LBW and hospitalisation
Illness				
Briegleb et al, 2015[80]	Secondary analysis of data on a population-based cohort of 31999 infant participants of a vitamin A RCT in urban and periurban/rural Tanzania, between 2010 and 2014.	LBW (2.01-2.50kg, ≤2.00kg) vs NLBW Preterm (<37 weeks) vs term (≥37 weeks) SGA vs AGA Overall and in urban v's periurban/rural settings	HR[1] for all cause hospitalisation in the first year of life	Overall: LBW: ≤2.00kg: 2.70 (1.77-4.14) 2.01-2.50kg: 1.05 (0.87-1.26) Preterm: 0.80 (0.64-1.00) SGA: 1.26 (1.05-1.50) No variation by urban vs periurban/rural areas
Le Roux et al, 2015[81]	Cohort of 697 infants in peri-urban South Africa, 2012-2014. Mothers enrolled at ANC	LBW vs NLBW Preterm vs term	IRR[5] for clinically diagnosed pneumonia in the first year of life	LBW:1.47 (0.95-2.20). Preterm: 1.52 (1.04-2.20)

Continued…

Table 1.3 continued

Citation	Study population & setting	Exposure	Outcome	Effect estimates (95%CI)
Kalanda et al, 2009[82]	Case control study of hospital born LBW infants with fetal anaemia & matched hospital born NLBW non-fetal anaemia controls, Malawi, between 1993 and 1995. Follow-up at the hospital at monthly intervals.	LBW fetal anaemia (35) LBW non-fetal anaemia (112) NLBW non-fetal anaemia (199)	IRR[5] of a) any illness, b) malaria, c) respiratory infection and d) diarrhoea Illnesses clinically diagnosed	**NLBW NFA:** a) 5.34 (4.99-5.69) b) 1.15 (0.99-1.31) c) 1.04 (0.89-1.19) d) 0.92 (0.73-1.11) **LBW FA** a) 4.67 (3.91-5.68) b) 0.83 (0.50-1.16) c) 0.82 (0.50-1.16) d) 0.76 (0.33-1.19) **LBW NFA:** a) 5.81 (5.33-6.34) b) 1.26 (1.03-1.49) c) 1.17 (0.95-1.39) d) 1.00 (0.73-1.29)
Kristensen and Olsen, 2006[83]	Cohort study of 571 infants in Soweto South Africa, followed to one year of age. Mothers recruited from 4 ANC clinics. HIV prevalence among pregnant women of 17%	LBW (1.70kg-2.49kg) Compared to infants weighing 2.50kg-3.49kg	Adjusted RR[3] for acute respiratory infections (ARI)	0.59 (0.51-1.31)

Continued…

Table 1.3 continued

Citation	Study population & setting	Exposure	Outcome	Effect estimates (95%CI)
Madhi et al, 2006[84]	Secondary analysis of 39836 infants enrolled in a pneumococcal vaccine RCT, South Africa, 1998, and followed up for 5 years. Outcome ascertained through hospital based surveillance	Preterm birth (<36 weeks GA & <32 weeks GA) vs term (≥36 weeks) (based on clinical records of GA)	RR[3] for hospitalisation for respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI) at <6mths, 6-12 mths, 12-24 mths, ≤5 years Bronchiolitis and pneumonia at <5 years.	<32w GA vs term <6m: 5.5 (3.6-8.3) 6-12m: 10.1 (6.1-16.5) >12-24m: 8.4 (4.6-15.4) <5y: 6.7 (5.0-8.9) <5y Bronchiolitis: 4.8 (3.0-7.7) <5y Pneumonia: 8.8 (6.1-12.6) 32-35w GA vs term <6m: 4.8 (3.7-6.3) 6-12m: 4.3 (2.7-6.8) >12-24m: 2.1 (2.7-6.8) <5y: 4.0 (3.2-5.0) <5y Bronchiolitis: 3.7 (2.7-5.1) <5y Pneumonia: 4.3 (3.2-5.9) <36w GA vs term <6m: 4.9 (3.6-6.3) 6-12m: 5.8 (4.1-8.3) >12-24m: 3.7 (2.3-6.0) <5y: 4.7 (3.9-5.7) <5y Bronchiolitis: 4.0 (3.0-5.3) <5y Pneumonia: 5.2 (4.0-6.7)

** Preterm<37 weeks' gestation, unless otherwise stated*

1 = hazard ratio; 2 = odds ratio; 3 = risk ratio; 4 = neonatal mortality rate; 5 = incidence rate ratio

1.6.4. Birth weight and mortality

Of the identified studies, only one (Katz et al)[52] used population-based data on gestational age and birth weight to generate mortality estimates beyond the neonatal period in subgroups of gestational age and size for gestational age. This study, a pooled analysis of data from 20 studies in 13 LMICs investigated the association between gestational age and mortality. It included data for 36636 infants from eight African studies published between 1997 and 2008 (two from Burkina Faso, one from South Africa, three from Tanzania, one from Uganda, and one from Zimbabwe). Of these eight studies, only three studies followed infants beyond six weeks of age, and only two to one year of age. The studies that followed infants beyond six weeks of age were all more than ten years old, and two included fewer than 2000 infants.

The pooled analysis of the African data indicated that, although preterm infants were at greatest risk of dying in the neonatal period, they remained at risk throughout the postneonatal period. Preterm infants were approximately seven times (risk ratio (RR)=7.19; 95%CI:4.12-12.52), two times (RR=1.99; 95%CI:1.49-2.66) and almost three times (RR=2.69; 95%CI:2.28-3.18) more likely to die in each of the neonatal, postneonatal and overall infant time-periods. SGA babies had a lower increased risk of mortality than preterm infants, but this risk persisted throughout the first year of life. SGA infants were roughly 1.5 times more likely to die in each of the neonatal (RR=1.62; 95%CI:1.14-2.26), postneonatal (RR=1.46; 95%CI:1.09-1.96) and infant periods (RR=1.52; 95%CI:1.21-1.91). Infants who were preterm SGA (equivalent to VLBW) had higher mortality rates in each time-period, and were approximately 12 times (RR=11.54; 95%CI:6.76-19.71), four times (RR=3.65; 95%CI:2.90-5.48) and five times (RR=4.75; 95%CI: 3.09-7.32) more likely to die in each time-period (**Table 1.3**).

These estimates are similar to those reported recently by Sania et al[68] (**Table 1.3**); although Sania reported higher infant mortality rates for preterm SGA (adjusted hazard ratio (aHR)=10.0; 95%CI:5.8-17.8). This recent study was not population-based as it recruited women who were seeking antenatal care, and so women and infants who were less likely to access care would have been underrepresented possibly leading to an underestimate of the association.

A limitation of both studies was their reliance on last menstrual period (LMP) and clinical assessment to determine GA. Approximately 90% of the infants in the study by Katz et al[52]

had their GA determined by clinical assessment and maternal recall of LMP. The study by Sania et al[68] used LMP. Ultrasound is considered the best method for assessing GA. There can be poor concordance between GA assessed by ultrasound and by either LMP or clinical assessment[85-87]. This may have caused misclassification of infants by GA which may have impacted on the estimates of the association between GA and mortality.

Recent estimates of the association between birth weight and postneonatal mortality in the general population (as opposed to populations recruited from for instance ANC clinics, such as the 2011 study by Bardaji et al[73], the 2005 study by Kuhn et al[79], and the 1996 study by Bloland et al[75] (**Table 1.3**)) are lacking. Those studies that recruited from the general population, such as Kayode et al[70,72], and Gladstone et al[78] did not generate estimates for the postneonatal period. Kayode et al[70,72] reported neonatal and under-5 mortality rates and Gladstone et al[78] reported mortality rates for infants between 6 weeks and 2 years of age (**Table 1.3**). In addition, to my knowledge, no studies have generated population-based estimates of the risk of mortality for VLBW for the entire infant period, even though the risk of mortality may be highest for these infants.

1.6.5. Birth weight and illness: evidence from SSA

Nine studies investigated the association between birth weight and infant illness in SSA (**Table 1.3**). All generated estimates beyond the neonatal period, three used population-based data, and three had more than 1000 participants. One generated estimates for infants weighing ≤2.00kg and one by subgroups of gestational age. Nonetheless, as will be explained in the following paragraphs, the results of these studies are conflicting, and overall there is a lack of robust evidence of how birth weight affects infant illness, especially when the evidence from Africa is compared to data from middle and high-income settings.

Five of the nine identified studies reported no association between birth weight and illness, clinic attendance or health facility admissions (an indicator of severe illness)[77-79,82,83].

In contrast, a secondary analysis of a population-based cohort of 31999 infants enrolled in a neonatal vitamin A trial from two sites (one urban and one peri-urban/rural) in Tanzania reported an association between both birth weight and preterm birth and hospitalisation. This study reported that infants weighing ≤2.00kg were 2.7 times more likely to be hospitalised in the first year of life compared to NLBW infants (aHR=2.70; 95%CI:1.77-4.14), but there was little evidence of an association for infants weighing 2.01-2.50kg. There was weak evidence that preterm infants had lower rates of hospitalisation (aHR=0.80;

95%CI:0.64-1.00) and some evidence that infants who were small for gestational age had moderately higher hospitalisation rates (aHR=1.26; 95%CI:1.05-1.50). These rates did not vary between the two sites. As the data on gestational age were based on maternal report of LMP, the estimates associated with preterm delivery and size for gestational age should be interpreted with caution as a) over 60% of enrolled infants were missing data on LMP, and b) gestational age as estimated by LMP is known to be discordant to that estimated using ultrasound, the gold standard method for gestational age assessment[88]. Furthermore, this study only analysed admissions to district hospitals, so infants suffering from severe illness were likely to be overrepresented.

Another secondary analysis of data on 39836 infants enrolled in a pneumococcal vaccine trial in an urban South African slum[84] reported that, in comparison to term infants, infants born at less than 32 weeks' gestation were 5.5, 10.1, 8.4 and 6.7 times more likely to be hospitalised for respiratory syncytial virus at each of <6 months of age, 6 to 12 months of age, 12 to 24 months of age and at <5 years of age (**Table 1.3**). They were five and nine times more likely to be hospitalised for bronchiolitis (risk ratio (RR) = 4.8; 95%CI:3.0-7.7) and pneumonia (RR=8.8; 95%CI:6.1-12.6) in the first five years of life. Elevated risks for these outcomes were also observed for infants of 32 to 35 weeks' gestation and for infants <36 weeks' gestation.

An association between preterm delivery and pneumonia was also reported by another small South African study of 697 infants born to mothers recruited from ANC[81]; although the evidence of an association with LBW compared to NLBW was weaker (Incidence rate ratio (IRR)=1.47; 95%CI:0.95-2.20).

Further evidence of how LBW and preterm delivery can increase the risk of illness comes from studies of hospitalised infants. An analysis of 208 infants with laboratory confirmed group B streptococcus (GBS) disease in Soweto, South Africa between 1997 and 1998[89] reported that both preterm birth and LBW were risk factors for both early (0-6 days of age) and late (7-90 days of age) onset invasive GBS. Preterm delivery was a risk factor for mortality from both early onset and late onset GBS, whereas LBW was identified as a risk factor for mortality from early onset disease only.

In summation, overall, the association between birth weight and infant illness has not been extensively studied in SSA, and the reported data are inconsistent, with some studies showing an association and others not. There is some evidence of an increased association

between birth weight and illness, but this mostly relates to severe illness (hospitalisation) or the data comes from hospitalised cohorts who are more severely ill.

1.6.6. Birth weight and illness: evidence from middle and high-income settings

Two studies from a middle-income setting (Brazil) reported that preterm, growth retarded and LBW infants are at increased risk of illness, including diarrhoea, vomiting, pneumonia and hospitalisation[90,91]. The first, a study of 4674 infants with known gestational age, recruited in southern Brazil in 1982[90], reported that in the first two years of life, growth retarded infants were more likely to be hospitalised for diarrhoea and pneumonia. Preterm infants were more likely to be hospitalised for pneumonia, but there was little evidence of an increased risk of hospitalisation for diarrhoea. A similar association between LBW and hospitalisation, diarrhoea and vomiting was found in a smaller study of 393 infants recruited in northeast Brazil in 1993[91], although no association was found with cough or fever, and there was no difference in rates of medical consultations.

The most compelling evidence that LBW is a risk factor for illness beyond the neonatal period comes from high-income settings. Data from a population-based record linkage study of 719311 live born singleton infants in Western Australia[65], reported that for every week reduction in gestational age below 39 completed weeks, the risk of infection related hospital admissions increased by 12%, and for every 0.50kg decrease in birth weight below 3.00kg, it increased by 19%. This is higher than the 9% increased risk of infection related hospitalisation per 0.50kg reduction in birth weight below 3.00kg reported for a population-based cohort of over 1.7 million infants from Denmark who were followed to 14 years of age[66]. In the Danish study infants weighing <1.00kg at birth were at increased risk of hospitalisation due to acute upper respiratory infection, viral pneumonia, bacterial pneumonia, septicaemia, and diarrhoea. The risk peaked in infancy.

These findings from high-income settings are not directly generalisable to African settings due to the overall poorer nutritional status, living conditions (crowding and poor access to water and sanitation) and access to health care in Africa, as well as the high burden of communicable diseases such as malaria. However, at the very least they suggest that the increased risk of illness among LBW infants, including infectious illness, is biologically plausible as it exists even in the absence of these risk factors for disease.

I will discuss the association between birth weight and VPDs in **Section 1.7**.

1.6.7. Birth weight and care seeking

One factor that may influence health outcomes for LBW infants is health care seeking behaviour. It has been reported that care seeking is influenced by perceptions relating to the severity of disease[92], and perceptions relating to the likelihood of survival of the infant[93]. A lack of care seeking for sick LBW infants may partially explain their increased risk of mortality.

Aside from the studies on the risk of hospitalisation (which is a marker for both care seeking and severe illness), few studies have actually investigated care seeking among LBW / preterm infants. Gladstone et al[78], in the aforementioned stratified cohort study from Malawi found no difference in the number of times that health care was accessed at 12, 18 and 24 months of age between preterm and term infants (p=0.86). One qualitative study from Uganda[94] reported that in the absence of weighing, mothers had poor recognition of LBW (especially among uniparous mothers who deliver at home). Many mothers did not recognise that LBW newborns were prone to illness, but they did know that they should seek care in the event of the infant falling ill. Other than these studies, I found no studies that specifically investigated whether birth weight was a determinant of care seeking in Africa.

Clearly much work needs to be done to better characterise the association between birth weight illness and care seeking in Africa.

1.7. THE IMPORTANCE OF VACCINATION OF LBW INFANTS

Given LBW infants' increased risk of mortality, and their possible increased risk of overall and infectious disease related morbidity, it is essential that they access all available preventative care services, including vaccination. Attendance for vaccination will not only protect them against vaccine preventable diseases, but it is a contact with the health services, and therefore an opportunity to diagnose illness and where indicated to access additional preventative and curative care services. Uptake of routine vaccination services may reflect an individual's overall uptake and access to care services, especially preventative care services. For instance, it has been shown that mothers who do not take their infants to vaccination services are also less likely to attend other preventative care services such as ANC clinics[95]. Delayed and under-vaccination of LBW infants may reflect a broader problem of reduced care seeking for these infants, when compared to NLBW infants.

Preterm infants may have immature immune systems leading to a lower primary antibody response to vaccination for certain vaccines such as the glycoconjugate vaccines (like those against Hib)[96]. Nonetheless, the majority achieve protective concentrations of antibody following vaccination[97]. Vaccination is considered as effective and safe in preterm and LBW infants as among term and NLBW infants[96,97], therefore with the exception of the HB vaccine (**Table 1.1**)[8], LBW infants should receive their vaccines at the same chronological age as term and NLBW infants[98].

In addition to a lower primary antibody response, vaccination of preterm infants in the first year of life generates antibodies that do not persist as long[96]. Consequently, the normal decline in antibody concentrations following vaccination may be of greater clinical significance in LBW infants[96,97]. It is therefore very important that they adhere to the schedule of both initial and booster doses of vaccine, and that they fully complete the schedule.

There are two additional reasons why prompt initiation of vaccination is important for LBW infants. Firstly, lower trans-placental maternal antibody transfer among LBW compared to NLBW infants[99,100] may increase their risk of infections with VPDs prior to vaccination. Secondly, although data on the risk of VPDs among LBW infants in SSA is lacking, data from high-income countries indicate that LBW and preterm infants are at increased risk of hospitalisation and death due to VPDs such as pertussis,[101] invasive pneumococcal disease[24,102,103] and Hib[104]. These diseases are most prevalent in the first few months of life[19,24]. Furthermore some of the complications of LBW, such as bronchopulmonary dysplasia may increase the susceptibility of LBW infants to the complications of pertussis[101].

Adherence to the full vaccination schedule, particularly to the initiation and timing of vaccination, may thus be even more important among LBW infants.

1.7.1. Guidelines for the vaccination of LBW infants

A number of organisations in high-income countries[98,105,106], and at least one in Africa (Kenya)[107] have specifically recommended that LBW infants receive their vaccines at the same chronological age as NLBW infants. In the WHO's online catalogue of immunisation policy recommendations[108], in particular in the section on contraindications to vaccination, the only recommendations relating to vaccination of preterm and LBW infants are in reference to HB vaccinations, where a modification to the routine schedule is indicated (**Table 1.1**). In previous policy documents, dating from the 1990s, prematurity and small for

date infants have been explicitly listed as being indicated for all vaccines[109]. A similar statement is not included in today's policy documents.

To my knowledge, there are no other current international guidelines on the vaccination of LBW infants, and the only international recommendations for the vaccination of these infants come indirectly from guidelines developed by WHO for the care of children in hospital in low income settings[110]. Hospital based care workers are advised to check a child's immunisation status prior to discharge and to administer any due vaccines. They are advised to vaccinate all children, including those who are sick or malnourished. They are also advised to communicate any outstanding issues, including those relating to vaccination, to the first-level health worker who referred the child and to advise the mother of the next due date for vaccination. Again, birth weight, size and illness are not listed as contra-indications to vaccination. These guidelines are not targeted at vaccine providers, only at infants admitted to hospital, thereby excluding the majority of infants.

A number of published papers[111,112] have stated that one country in Africa, Guinea Bissau, had a policy of delaying the administration of BCG vaccination to LBW infants. They have given no details of this policy, nor have they provided references for the policy. I have not been able to access any official government documents relating to this, and so I have not been able to verify this.

1.7.2. Adherence to the vaccination schedule among LBW infants

Several reports from middle and high-income settings have indicated that adherence to the routine schedule is worse among LBW infants compared to NLBW infants[40,113-118], that they are more likely to be vaccinated later than term infants, especially for first dose OPV and DTP[115], and that vaccine-specific timely vaccination rates are 3% to 15% lower for LBW[116] than NLBW infants. A study of 112 parents of preterm infants who were attending a neonatal follow-up clinic in the USA reported that the majority of parents of LBW infants were unaware their infants are supposed to be vaccinated at the same chronological age as NLBW infants and the parents believed that the decision to initiate vaccination depends on the degree of prematurity of the infant and the infant's weight[119]. It has also been reported that vaccine providers in the United States are reluctant to vaccinate infants who weigh less than 4.50kg at the time of vaccination, or who suffer from underlying conditions such as bronchopulmonary dysplasia or apnoea of prematurity[120].

Few studies have directly investigated uptake or timing of vaccination in LBW infants in SSA. In addition to the analyses I have carried out as part of this thesis, I am aware of only one other study in Africa that has directly addressed this issue.

This 2015 study[121] from two informal urban settlements in Nairobi, Kenya, used data on 3602 of 8756 infants enrolled in a health and demographic surveillance system between 2006 and 2013 to investigate time to BCG vaccination. Vaccination of LBW infants (categorised as 2.00-2.49kg and <2.00kg) was compared to that of NLBW infants, between 0 and 90 days of age, using log normal accelerated failure time parametric modelling. Birth weight data was based on what was documented at birth on the child health card. In this study, only BCG vaccinated infants surviving to at least 90 days of age, and whose vaccination card was seen after 90 days of age, were included. Only BCG vaccinated infants were included in the analysis. If LBW infants were less likely to be vaccinated, the effect of birth weight on time to vaccination would be underestimated. The prevalence of LBW in the sample was very low (6%). A high percentage (96%) of infants were born in health facilities, and 67% of those born in health facilities were born in private facilities. This study reported that 60% of LBW infants received BCG at >5 weeks of age. Infants weighing 2.00-2.49kg took 1.4 times longer (time ratio (TR)=1.44; 95%CI:1.15-1.82) to be vaccinated than NLBW infants. Those weighing <2.00kg took 9 times longer (TR=8.97; 95%CI:6.01-13.39). The authors also reported that infants born in public compared to private facilities were vaccinated sooner (TR=0.48; 95%CI:0.44-0.53). The association between birth weight and BCG vaccination varied by place of delivery. When compared to NLBW infants, infants weighing <2.00kg who were born in private health facilities took much longer to be vaccinated than those born in public facilities (adjusted TR (aTR)=14.41; 95%CI:10.06-20.64 versus aTR=1.79; 95%CI:1.27-2.54), as did infants weighing 2.00-2.49kg (aTR=3.66; 95%CI:1.78-7.50 for those born in private facilities; aTR=1.18; 95%:0.88-1.59 for those born in public facilities). Therefore, in this study, being born in a private health facility appeared to be a major driver of the association between LBW and vaccination. The authors stated that the WHO BCG vaccination position paper[9] recommended vaccinating preterm infants at >40 weeks, and that this may underlie the delay observed in their study population. However, no such recommendation is made in the position paper. The position paper[9] states that all infants should be vaccinated in the neonatal period, and that the only contraindications to BCG vaccination are symptomatic HIV infection and exposure to a smear positive pulmonary tuberculosis (TB) patient.

A number of additional studies have provided indirect evidence that LBW infants could be at risk of under-vaccination. An analysis of 5171 infants attending for BCG vaccination at four health centres in urban Nigeria[122] indicated that compared to children who were not undernourished, undernourished children (two standard deviations below either the normal z-scores for weight for age or height/length for age or for body mass index) were 1.7 times more likely to attend for vaccination at more than two weeks of age (aOR=1.70; 95%CI:1.45-2.09) and six weeks of age (aOR=1.74; 95%CI:1.45-2.09). This study did not explicitly investigate the association with birth weight and BCG vaccination. As LBW is one of several contributory factors, along with feeding practices and illness, to undernourishment, these results cannot be taken as directly indicative of an association with birth weight[123]. In addition, the authors did not find an association between preterm delivery and BCG vaccination.

A study investigating the effect of early DTP vaccination on mortality in LBW infants in Guinea-Bissau reported that compared to LBW infants who were vaccinated with DTP1 at two months of age, those LBW infants who were unvaccinated had poorer anthropometric status (including mean birth weight, mean weight gain between enrolment and two months of age, mean weight at two months of age, mean weight for age z score, mean length at two months, mean height for age z score, mean mid-upper arm circumference, mean head circumference and mean abdominal circumference)[112]. Although this study made no comparison to NLBW infants, it does suggest an association between severity of LBW and vaccination.

Another study from Guinea Bissau[111] of 7138 infants born at hospital between 1989 and 1999, reported that LBW infants had lower BCG uptake rates until 18 months of age, compared to NLBW infants. However, as explained in **Section 1.7.1,** the authors stated that in Guinea Bissau there was a policy of not vaccinating LBW infants at birth, and mothers were instead advised to return for BCG vaccination, either when the child had gained weight or at the scheduled visit for DTP/OPV vaccination at six weeks of age. Given this policy, these results are not generalisable to other African populations where no such policy exists. Again these authors cited a WHO policy of delaying BCG vaccination until 40 weeks; however as stated in **Section 1.7.1**, no such recommendation appears to be given in the document[109].

A review of unpublished grey literature studies from low income settings identified thirteen studies reporting parental reluctance to bring sick, weak or malnourished children for

vaccination for reasons of social stigma and fatalism[124]. In this review, an additional 47 studies reported false contra-indications (including infant illness and weight) as reasons for non-vaccination cited by both vaccine providers and parents[124]. Infant illness is repeatedly cited in the grey literature as a reason for non-vaccination, with health workers in Kenya, Nigeria, Pakistan and many other places citing this as a contra-indication to vaccination[124]. In a study of health workers and mothers in Mozambique, 40% of mothers and many health workers reported that they would not accept vaccination of a child with fever. It has also been reported that children who are perinatally infected with HIV are less likely to be up-to-date with their vaccines at 12 and 24 months of age than HIV-exposed uninfected children[125].

In addition, it has been reported that parental perceptions of the likelihood of survival of an infant are known to influence the decision to seek curative care[93]. These perceptions may also influence the decision to seek preventative care such as vaccination services. This attitude may be more common for fragile, small LBW infants, and may be more common for infants with additional barriers to vaccination, such as poorer infants born to uneducated mothers[47].

Given their potential increased risk of infectious disease related illness and mortality and their increased risk of being vaccinated late, LBW infants may be under-served by routine vaccination services, and may be a high-risk group for under-vaccination.

1.7.3. Capturing under-vaccination of LBW infants using routine methods of vaccine programme evaluation.

As discussed **in Section 1.4**, routine estimates of vaccine uptake report on uptake at 52 weeks of age using all infants alive at 52 weeks of age as the denominator (except for vaccines given at birth, like BCG, which use all live born infants as the denominator)[12]. These estimates will not illustrate poorer uptake rates among infants who die before 52 weeks of age. Thus they are unlikely to accurately reflect uptake rates among infants, such as LBW infants, who are at higher risk of mortality in the first 52 weeks of life, or who due to their fragility are more likely to be delayed in getting vaccinated. LBW infants who survive to one year of age will mostly catch-up in their growth and may largely resemble NLBW infants, including in terms of their vaccination status. As they gain weight over time, and become less fragile, their mothers may be more likely to bring them for vaccination.

1.7.4. Improving uptake of vaccination of LBW infants

Exploiting routine contacts with health care providers at vaccination clinics and other contacts with the health service could provide a convenient and cost-effective way of increasing timely vaccination among both LBW infants and other infants who are under-served by vaccination. This is in accordance with the recommendations of the latest Global Vaccine Action Plan[4] which, as discussed in **Section 1.5**, advocates that all contacts with health care providers should be used as opportunities to verify an infants' vaccination status and to vaccinate when indicated.

1.8. METHODS TO ASSESS OPPORTUNITIES FOR VACCINATION.

In the literature, opportunities are typically defined as a contact with a health care provider that could be used to administer a vaccine for which an infant is eligible[41,126-134]. Opportunities are usually counted from the date the infant becomes eligible for receipt of the vaccine[41,127]. The denominator for analyses of opportunities for vaccination has variously been all surveyed children[126,127] or children having opportunities[16,41].

1.8.1. The use of opportunities to improve vaccination in SSA

A number of studies[16,41,126-132,134,135] have investigated the potential of using opportunities to improve the delivery of vaccines in SSA. All but two of these studies are more than twenty years old, and none have specifically looked at groups that are under-served by vaccination, such as LBW infants. These studies include one systematic review dating from 1993[129], four analyses of vaccine coverage data[16,41,126,127], and six facility-based surveys[128,130-134]. Most of these studies are descriptive in nature; only one study has investigated risk factors for missed opportunities[127].

An analysis of DHS data collected between 1996 and 2005 on 217706 children from 45 LMICs, including 25 countries from SSA, reported that 29% to 82% of all opportunities for vaccination were missed[16]. In SSA, the percentages of missed opportunities reported in this study ranged from 17% to 71%.

A community based cross-sectional survey of 668 randomly sampled children aged <2 years conducted in 1992 in Mozambique[127] reported that 25.7% of children had experienced a missed opportunity for vaccination. Children had a mean of 1.73 opportunities each. This was the only study that quantitatively analysed determinants of vaccination. It identified facility birth (aOR=2.29; 95%CI:1.37-3.83) and mothers being single, divorced or widowed

(compared to married or cohabiting) (aOR=1.68; 95%CI:1.07-2.64) as predictors of missing opportunities.

A population-based national vaccine coverage survey of 642 children aged 12 to 23 months, conducted in the Central African Republic in 1990[41] reported that 61% of opportunities for DTP1 vaccination, 62% for DTP2 vaccination and 70% for measles vaccination were missed. For each of these respective vaccines, 19%, 11% and 28% of all opportunities occurred when another vaccine was given. Had all opportunities been exploited, the coverage of all scheduled doses would have increased by 74% (from 34% to 59% at 21 months of age) and the days at risk of contracting measles would have declined by a mean of 74 days per subject.

Cutts et al[126], analysed data from seven community based vaccine uptake surveys in Mozambique and one in Conakry, Guinea, conducted between 1987 to 1989. These surveys included qualitative interviews with mothers on their knowledge, attitudes and practices relating to vaccination. The authors reported that, among those with vaccination records, 19% of children in Conakry, and 6% of children in Mozambique would have been fully vaccinated if all contacts with health care providers had been used to vaccinate.

A 1991 review of studies of missed opportunities for vaccination from 45 countries, including 19 studies from 15 African countries[129], reported that a median of 41% of children (range 0-99%) in developing countries had missed opportunities for vaccination. The review reported that missed opportunities in developing countries (based on an analysis of 10 studies) were more common at curative care visits (median prevalence = 42% (range 14-91%)) than preventative care (median prevalence = 32% (range 2-54%)) visits. The study also described the reasons for missing opportunities. These include failure to administer vaccines simultaneously, false contraindications to vaccination, fear of wasting vaccine by opening a vial for a small number of children, lack of assessment of vaccination status when the child visited a clinic, vaccine shortages, poor organisation of vaccine clinics, and a lack of a daily vaccination clinic.

A study[133] of missed opportunities for vaccination in Sudan, included a qualitative component whereby mothers exiting the clinic were asked about why a child had not been vaccinated. Mothers reported refusing vaccination if their child was ill. This has also been reported as a reason for non-vaccination by both mothers and vaccine providers[124], as

previously discussed. Given the greater fragility and possible increased incidence of illness in LBW infants, it may be that they are more likely to miss opportunities for vaccination.

In summary, studies have reported that opportunities for vaccination exist and that many of these opportunities are missed. There is however a lack of up-to-date information on the frequency, use, and potential impact of such opportunities to improve the timely delivery of vaccines in Africa. In particular, the potential of using such opportunities to improve the vaccination of LBW infants has not been investigated.

1.9. RATIONALE FOR THE PHD

It is evident that a number of important gaps exist in the data relating to LBW infants in SSA. There is a paucity of population-based estimates of mortality and illness for LBW infants in SSA, in particular in the postneonatal period, and in particular for VLBW infants (as discussed in **Section 1.6**). Access to care seeking and preventative care services for these infants in SSA have been poorly described. There has been little direct research into whether they are an under-served group for vaccination (as discussed in **Section 1.7**), and into how to improve their vaccination by utilising routine health care contacts as opportunities for vaccination (as discussed in **Section 1.7.4**). Data on how the association between birth weight and these outcomes relate to or are influenced by other socio-demographic factors are lacking.

Between June 2010 and January 2013, a large trial to assess the impact of neonatal vitamin A supplementation on infant mortality was conducted in the Brong-Ahafo region of Ghana. The Neovita trial (described in detail in **Chapter 2**) recruited almost 23,000 infants from a population-based pregnancy surveillance system. High quality data on birth weight and vaccination were collected on all infants enrolled in the trial. As the trial epidemiologist this afforded me an excellent opportunity to address these specific gaps in the evidence, particularly in relation to LBW infants' access to routine vaccination.

1.10. PHD AIMS AND OBJECTIVES

Overall in this PhD, I aimed to investigate whether LBW is a risk factor for under-vaccination among infants in Ghana; to frame their access to vaccination services within the broader context of their risk of mortality, illness, failure to seek care, and health facility admissions; and to investigate ways to improve their vaccine uptake.

With this in mind, I defined four overall objectives for the PhD (which will be further detailed and expanded upon in the corresponding papers in **Chapters 4 to 7**). These are:

1. To assess whether LBW was a determinant of mortality, illness, care seeking, and health facility admission in the first year of life, and in each of the neonatal, early and late infant periods.

This was addressed by:

a) Quantifying the association between birth weight and mortality and illness, and among those reporting illness, generating estimates of the association between birth weight and care seeking, and health facility admissions in the first year of life.
b) Investigating how these estimates varied between the neonatal, early and late-infant periods
c) Assessing whether the association between birth weight and mortality varied by distance to the nearest health facility, and by SES.

2. To investigate birth weight and other factors as determinants of the timeliness of postneonatal vaccination (using DTP1 and DTP3 as indicator vaccines).

This was addressed by:

a) Assessing whether LBW was a determinant of DTP1 and DTP3 vaccination
b) Assessing whether maternal education or SES modified the association between birth weight and vaccination with DTP1 and DTP3
c) Quantifying other determinants of delayed DTP1 and DTP3 vaccination

3. To investigate birth weight and other factors as determinants of neonatal BCG vaccination.

This was addressed by:

a) Evaluating whether birth weight was a determinant of neonatal BCG vaccination
b) Assessing whether the association between birth weight and neonatal BCG vaccination varied by place of delivery or infant illness
c) Quantifying other determinants of neonatal BCG vaccination

4. To investigate the potential for using routine contacts with health care providers to improve vaccine uptake, including among LBW infants, and to assess whether birth weight and other factors were determinants of uptake of opportunities.

This was addressed by:

a) Quantifying the number and types of opportunities for vaccination, and the associated missed opportunities for vaccination in the first year of life
b) Identifying the determinants of uptake of those opportunities
c) Assessing how using the first opportunity for vaccination could increase the uptake of vaccines included in the routine childhood immunisation schedule.

1.11. THESIS STRUCTURE

This thesis is structured as a thesis by publication. In **Chapters 2 and 3** I present the methodology for both the Neovita trial and for the PhD. This is followed by a results section comprising four chapters (**Chapters 4 to 7**) presenting four papers that have been, or are in the process of being published in peer-reviewed scientific journals. When applicable, I provide additional materials, such as further details of the methods, results and further discussion that were not included in the published papers. I close with a final section comprising a chapter (**Chapter 8**) presenting an overall discussion of, and conclusions from the research findings. This includes a critique of the strengths and limitations of the research, an assessment of the implications of the findings for public health policy, and recommendations arising from these findings.

1.12. ROLE OF THE CANDIDATE

I was the trial epidemiologist on the Neovita trial, within which this PhD was nested. I was a member of the trial management team, and I was based in the field in Kintampo, the location of the trial, for the three-year duration of the trial. Whilst in Kintampo, I managed the collection of the trial data (subsequently used in this PhD). I played an integral role in all aspects of trial management, with major contributions to the training of field staff, supervision of field work, development and operation of the data management system, supervision of data management, preparation of datasets for the trial analysis, and analysis, write-up and dissemination of the trial findings. I took lead responsibility for ensuring the quality of the data collected for the trial, including the vaccination data used in this PhD. I remained as the trial epidemiologist after I registered for this PhD.

With the help of my supervisors, I developed the concept for the PhD, and I designed the analytical plans for each of the analyses. I developed the datasets for the analyses,

conducted all the analyses, and drafted all the papers, with input from my supervisors, statistical advisor and co-authors. Similarly, I also wrote all the supporting PhD chapters.

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CHAPTER 2: OVERVIEW OF THE NEOVITA TRIAL AND ITS METHODOLOGY

Preamble

This chapter presents an overview of the methods of the Neovita trial, including a description of the setting of the trial (Ghana), the study area, the trial design, an overview of the recruitment and data collection processes, and a description of the process of data management.

2.1. THE NEOVITA TRIAL

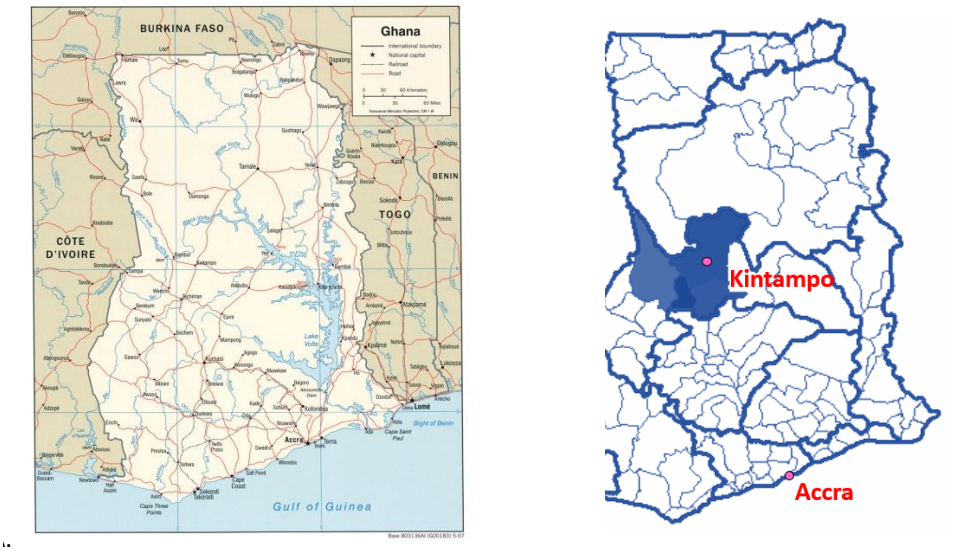
Neovita was a randomised double blind placebo controlled trial, undertaken in the Brong Ahafo region of Ghana between June 2010 and January 2013. Neovita aimed to assess the impact of neonatal vitamin A supplementation (50,000 IU) on all-cause mortality at four, 26 and 52 weeks of age.

A team from the Faculty of Epidemiology and Population Health at the London School of Hygiene & Tropical Medicine (LSHTM), in partnership with the Kintampo Health Research Centre (KHRC), conducted the trial. I was the epidemiologist on the trial and I explain my role in Neovita in **Section 1.12**. The trial protocol and results have been published[1,2].

2.2. GHANA, THE SETTING OF THE NEOVITA TRIAL

Ghana is situated in the Gulf of Guinea in West Africa (**Figure 2.1**) and has an estimated population of 24.7 million people, including an estimated 3.4 million children aged less than 5 years[3]. The gross national income per capita is approximately $1550 and 29% of the population live below the national poverty line. The current life expectancy at birth is 61 years[4].

Figure 2.1: Map of a) Ghana[5] and b) the Neovita study area



2.2.1 Mortality rates and neonatal and postneonatal cause of death

The 2013 under-5 mortality rates in Ghana, overall, and in each of the early neonatal, late neonatal, postneonatal, and childhood periods, have been estimated (**Table 2.1**)[6].

Table 2.1: Under-5 mortality per 1000 live births by time-period, Ghana, 2013[6].

Time-period	Mortality rate per 1000 live births (95%CI)
Early neonatal (0-6 days)	21.9 (19.1-24.8)
Late neonatal (7-28 days)	5.9 (5.1-6.8)
Postneonatal (29-364 days)	18.3 (14.9-22.1)
Childhood (1-4 years)	27.2 (21.5-34.2)
Under-5 years	71.4 (62.4-82.3)

Mortality remains high throughout the postneonatal period and childhood. Little change in this rate is projected to occur by 2035[7]. There is also considerable variation in mortality by geographic region (**Figure 2.2**). In Brong Ahafo, the neonatal mortality rate is estimated to be 27 per 1000 live births in the neonatal period, 10 per 1000 live births in the postneonatal period, 38 per 1000 live births in the infant period and 57 per 1000 live births among under-fives[8], lower than for most other regions in Ghana (**Figure 2.2**).

Almost 70% of deaths among infants aged 1 to 59 months were estimated to be due to infectious causes[7] (**Figure 2.3**). Most deaths in the neonatal period were due to non-infectious causes such as intrapartum complications. VPM data is subject to several limitations[9-11], including the potential for misclassification of cause of death[10,11], so these data should be interpreted with caution.

Figure 2.2: Under-five mortality rate, stratified by time-period and geographical region, Ghana, 2014[8].

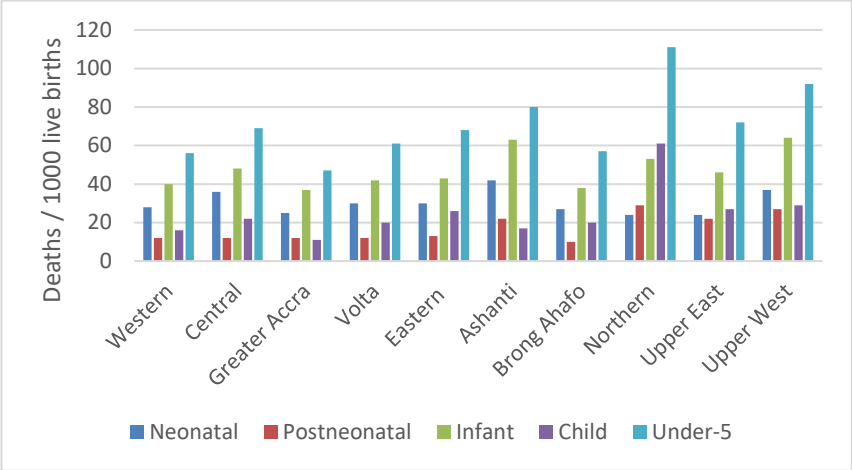
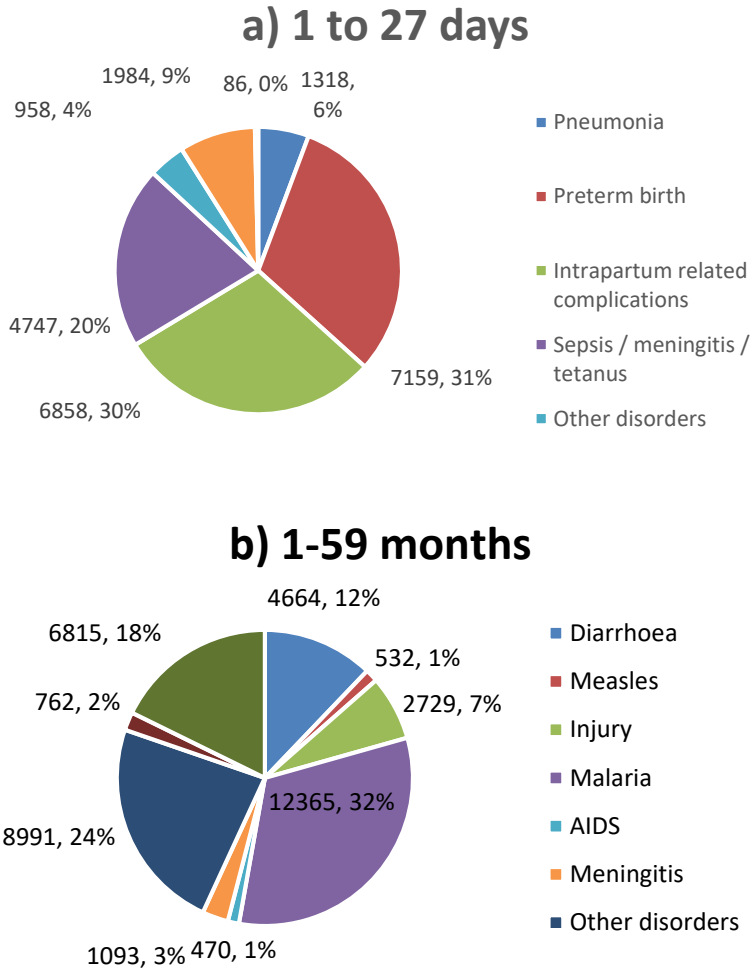


Figure 2.3: Estimated cause-specific under-5 mortality from a) 1-27 days, and b) 1-59 months, Ghana, 2013*.



* *Modified from Liu et al, 2015*[7]

There is a lack of population-based data on neonatal and postneonatal cause of death in Ghana. Neonatal and postneonatal cause of death data are available from two health and demographic surveillance (HDSS) systems in Dodowa (near Accra) and Navrongo (Northern Ghana); although there is considerable variation in the rates reported at each site (**Table 2.2**)[12]. Cause-specific mortality was consistently higher in Navrongo compared to Dodowa, which reflects its higher infant (40 versus 18 deaths/1000 live births) and under-5 (75 versus 41 deaths/1000 live births) mortality rates. The neonatal mortality incidence rate due to prematurity was high in both sites, but particularly in Navrongo. In both sites the most common cause of postneonatal mortality was pneumonia.

Table 2.2: Neonatal and postneonatal cause cause-specific mortality rates per 1000 person years of follow-up, Dodowa and Navrongo Health and Demographic Surveillance Systems[12].

	Cause of Death	Dodowa (2006-2012)	Navrongo (2000-2012)
Neonatal	Birth Asphyxia	11.17	52.57
	Neonatal Infections	15.45	43.80
	Congenital abnormalities	-	0.95
	Prematurity	5.94	57.14
Postneonatal	Diarrhoea	0.51	3.14
	HIV/AIDS	0.39	0.99
	Malaria	0.36	2.59
	Pneumonia	3.47	4.93
	Other Infections	0.23	2.09

2.2.2. Burden of low birth weight and vaccine preventable diseases

Data from the most recent DHS[8] indicated that approximately 10% of infants born in Ghana are LBW; although birth weight data were only available for 60% of infants[3]. To my knowledge, there are no available data on the incidence of VPDs in Ghana. In 2014 there were a total of 151 cases of VPDs reported; 124 of measles, 26 of rubella, and 1 of tetanus; undoubtedly a gross underestimation of the true burden of VPDs in the country[13].

2.3. ORGANISATION OF VACCINATION SERVICES IN GHANA

2.3.1. The infant vaccination schedule in Ghana

Routine vaccination in Ghana is delivered by the Ghana Health Service (GHS) through the Expanded Programme on Immunisation (EPI) according to a standardised schedule[14] (**Table 2.3**).

Table 2.3: Recommended schedule for the delivery of childhood vaccines in Ghana[14].

Scheduled Vaccine	Birth	6 weeks	10 weeks	14 weeks	9 months
BCG	Y				
Polio	Y	Y	Y	Y	
DTP/HiB/HepB†		Y	Y	Y	
Pneumococcal*		Y	Y	Y	
Rotavirus*		Y	Y		
Measles					Y
Yellow Fever					Y

† Given as a single injection and hereafter referred to as DTP
** Introduced in May 2012*

2.3.2. Organisation of vaccination services

Vaccines that are scheduled to be administered at birth (BCG and birth OPV) are usually given to infants born in health facilities (hospitals, maternity homes and community based health facilities) before they leave the facility following delivery. Women attending ANC are advised to bring their infants for vaccination after birth, and traditional birth attendants (TBAs) and community based surveillance volunteers (CBSVs) have been trained to advise mothers delivering at home to bring their newborns for vaccination. Consequently, infants born at home should be taken to child health clinics to get these vaccines. Vaccines scheduled for administration in the postneonatal period are given at child health clinics.

Child health clinics are held at health facilities, but also at Community Health Planning System (CHPS) compounds in the community and are delivered by vaccine-providers (both community health nurses and community health officers). In addition to these clinics, mobile teams hold clinics at outreach points in the community. These mobile clinics target areas that are not served by a static health clinic, that are hard-to-reach or that have low vaccine uptake. Private health facilities such as private maternity homes increasingly deliver vaccines, and those that do are integrated within the routine system for vaccine procurement, delivery and reporting.

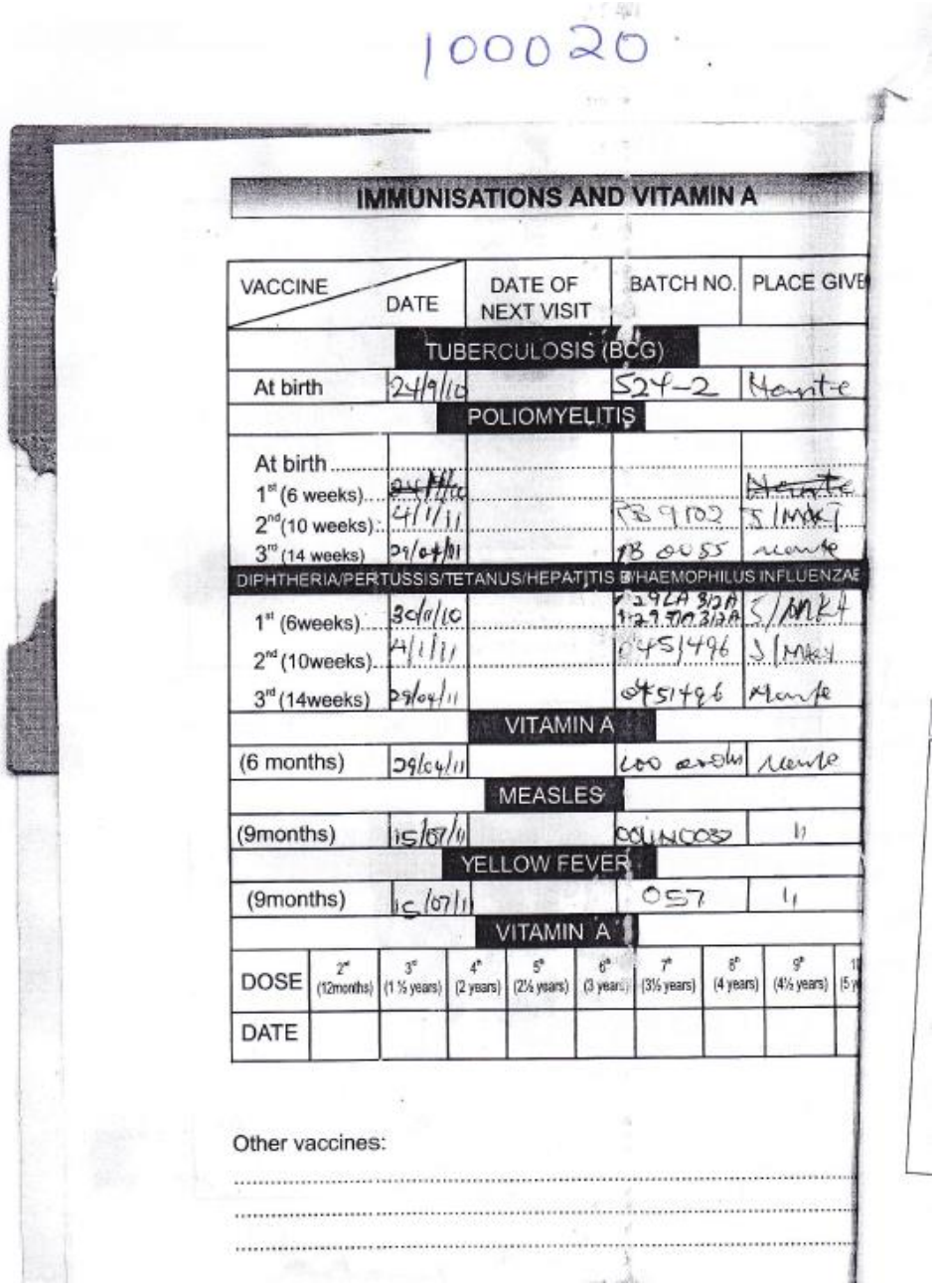
2.3.3. Documentation of vaccination

Staff at the child health clinics and private facilities record all vaccines administered, including the date, the place of administration and the vaccine batch number, usually in the infant's child health book (**Figure 2.4**).

These data may also be documented on a vaccination card or in the mother's antenatal card. The staff advise the mother of the next scheduled date for vaccination. Staff refer to

these cards to determine what vaccines need to be administered. The clinics also retain their own registers of what vaccines were given to whom at each clinic. If the child never attends for vaccination, the child may not be in possession of a vaccination card.

Figure 2.4: A typical vaccination record from Ghana



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IMMUNISATIONS AND VITAMIN A

VACCINE / DATE	DATE OF NEXT VISIT	BATCH NO.	PLACE GIVE
TUBERCULOSIS (BCG)			
At birth	24/9/10	524-2	Hante
POLIOMYELITIS			
At birth			
1st (6 weeks)			
2nd (10 weeks)	4/1/11	[illegible] 9102	S/MK
3rd (14 weeks)	29/04/11	[illegible] 00 55	Hante
DIPTHERIA/PERTUSSIS/TETANUS/HEPATITIS B/HAEMOPHILUS INFLUENZAE			
1st (6weeks)	30/8/10	[illegible]	S/MK
2nd (10weeks)	4/1/11	045/496	S/MK
3rd (14weeks)	29/04/11	045/496	Hante
VITAMIN A			
(6 months)	29/04/11	100 [illegible]	Hante
MEASLES			
(9months)	15/07/11	[illegible]	11
YELLOW FEVER			
(9months)	15/07/11	057	11
VITAMIN A			

DOSE	2e (12months)	3e (1 ½ years)	4e (2 years)	5e (2½ years)	6e (3 years)	7e (3½ years)	8e (4 years)	9e (4½ years)	10 (5 y
DATE									

Other vaccines:

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2.3.4. Supplementary Immunisation Activities

In addition to these routine vaccination activities, supplementary immunisation activities (SIAs), primarily targeting polio, but also targeting measles, are conducted. These involve mobile vaccination teams visiting communities and going from house to house to offer vaccination. The administration of these vaccines is not documented. These vaccines are

given in addition to, and not in lieu of the routinely scheduled vaccines. The SIAs conducted in Ghana during the trial period are summarised (**Table 2.4**).

Table 2.4: Summary of supplementary immunisation activities in Ghana during the trial period.

Year	Supplementary immunisation activity	Level	Dates
2010	Integrated measles / vitamin A campaign	National	3rd – 6th November
2011	National polio immunisation days	National	24-26 March
	Ghana Integrated Child Health Campaign (Polio, vitamin A & de-worming)	National	12-14 May
	National polio immunisation days	National	27-29 October
	Yellow fever campaign (Kintampo North & South)	District	22-28 November
2012	National polio immunisation days	National	22-29 March

There was one national measles campaign in 2010, three national polio SIAs and one district level yellow fever SIA in 2011 and one national polio SIA in 2012. For polio these SIAs are held as part of the drive towards polio eradication. SIAs for other vaccines are held to either boost uptake, or as exemplified by the yellow fever campaign conducted in the study area in 2011, part of disease control measures in response to outbreaks of specific VPDs.

2.3.5. Evaluation of the routine childhood vaccination programme

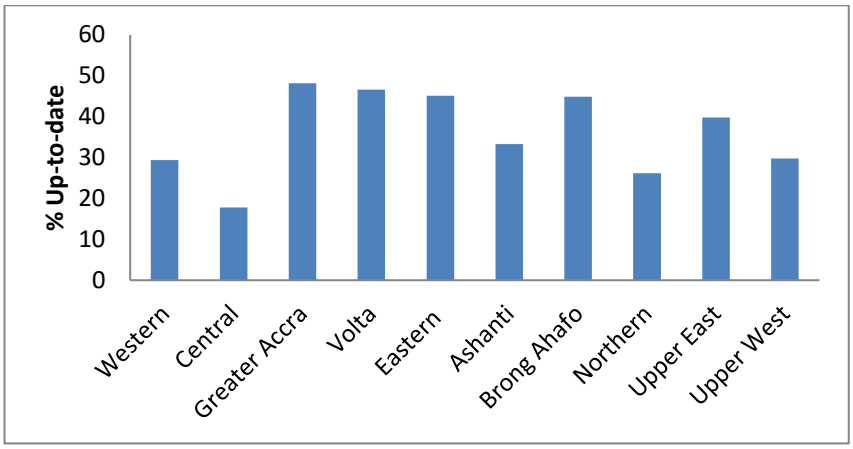
The routine childhood vaccination programme in Ghana is evaluated by WHO, UNICEF and other international organisations using the standard indicators recommended by WHO and UNICEF[15,16], including vaccine uptake for all vaccines at 52 weeks of age and drop-out rates. These data are compiled using monthly returns on vaccines administered at all child health clinics. The reported data from Ghana is subject to all the limitations associated with registry and survey data for estimating uptake as previously described in **Section 1.3**[17].

2.4. UPTAKE, TIMING AND DETERMINANTS OF VACCINATION IN GHANA.

Vaccination uptake is improving annually. The 2014 Ghana DHS reported 52 week uptake rates among children aged 12 to 23 months of over 95% for BCG and DTP1 and of over 85% for three doses of polio and DTP[3]. However, deficiencies in vaccine delivery remain. For instance, only 51% of infants aged 12-23 months were reported to have been fully vaccinated (received all of the recommended doses in the routine schedule), and this varied considerably with geographic location (**Figure 2.5**). Brong Ahafo had some of the highest

rates of up-to-date vaccination in Ghana. However, only 71% had received all their basic vaccinations (BCG, measles and three doses each of OPV and DTP)[8].

Figure 2.5: Percentage of children aged 12-23mths who were fully vaccinated by geographic region, Ghana 2014.



Adapted from the Ghana DHS 2014[8]

Previous research from Ghana (and from the Neovita study area) indicates that many infants receive their vaccines over four weeks late (20% for BCG and measles vaccine and 40% for the final dose of polio vaccine)[18]. Low socioeconomic status, low maternal educational attainment and rural place of residence have all been found to be associated with delayed vaccination[18]. The association with birth weight has not been studied.

2.5: THE NEOVITA STUDY AREA

Figure 2.6: The study area

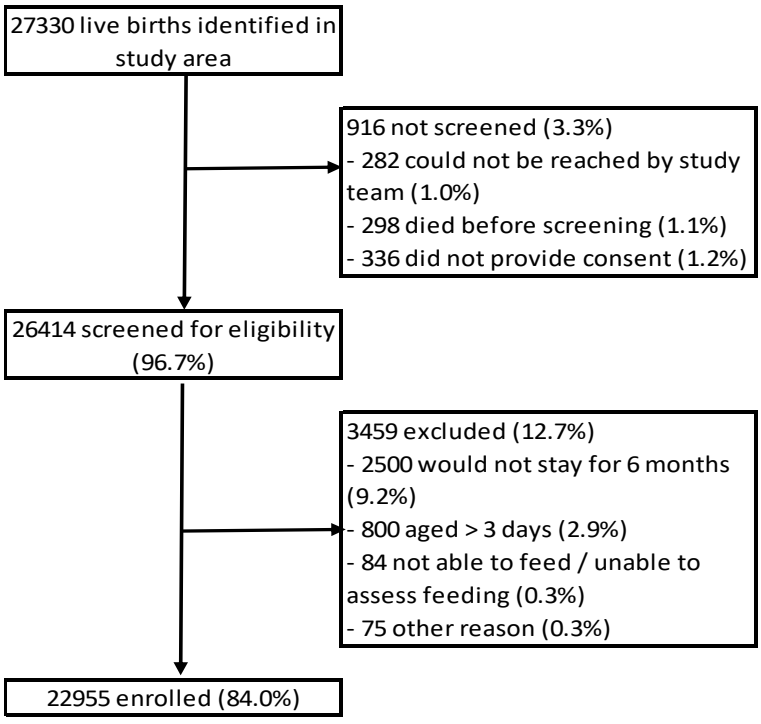
Brong Ahafo is the second largest region in Ghana and has an estimated population of 2,310,983[3]. The largest ethnic group in the area is Asante. Twi is the main language spoken. The population is widely dispersed, clustering in small villages of primarily mud compounds. Subsistence farming and small-scale trading are the primary sources of income.

The Neovita study area has an estimated size of 12,000 square kilometres and is comprised of seven contiguous districts (Kintampo North, Kintampo South, Nkoranza North, Nkoranza South, Tain, Techiman and Wenchi) (**Figure 2.1).** The estimated population in these districts is over 600,000, including an estimated 120,000 women of reproductive age[1]. The study area is served by four district hospitals and 69 fixed site health facilities.

2.6. ELIGIBILITY CRITERIA FOR NEOVITA

Enrolment into Neovita was restricted to those infants who i) were going to stay in the study area for at least 26 weeks post-dosing; ii) were aged three days old or less at the time of enrolment and iii) were well enough to suck or feed and therefore to receive an oral dose of vitamin A or placebo. The number of infants screened, excluded and enrolled in Neovita is summarised (**Figure 2.7**), and the process for their screening and enrolment is described in **Section 2.7**. Of 27330 live births identified in the study area, 26414 (94.7%) were screened for inclusion in Neovita and 22955 (84.0%) were enrolled.

Figure 2.7: Recruitment and enrolment of infants in the Neovita trial, Ghana 2010-2013*.



** Percentages are of all live births*

2.7. RECRUITMENT

For the trial, village based fieldworkers enumerated all compounds in the study area and visited them at 12 week intervals to identify women of reproductive age (aged 15 to 49 years). The fieldworkers registered all women who were planning to remain in the study area for at least 26 weeks in a reproductive surveillance system, allocated them a unique anonymous identification number and visited them at 12-week intervals to determine if they were pregnant. The fieldworkers visited pregnant women every four weeks during their pregnancy and daily during their final month of pregnancy to ensure prompt identification of all births (**Figure 2.8**).

Newborns were screened for enrolment in Neovita by trained dosing supervisors who visited all villages and health facilities in their area daily to ascertain births. They worked with a network of key informants in the community (surveillance field workers, TBAs, health facility staff and CBSVs) to identify births promptly. All infants born at home or in a health facility were screened for enrolment in the trial and informed written consent was obtained from all mothers prior to enrolment. Each enrolled infant was allocated a unique anonymous identification number and dosed with either vitamin A or a placebo by the dosing supervisors. Infants were visited at day one and three post-dosing and at four weekly intervals for the first 52 weeks of life or until their vital status at 52 weeks of age was determined (**Figure 2.8**).

Fieldworkers were directed to visit compounds, registered women, pregnant women and infants at set intervals using automated weekly listings distributed to all fieldworkers.

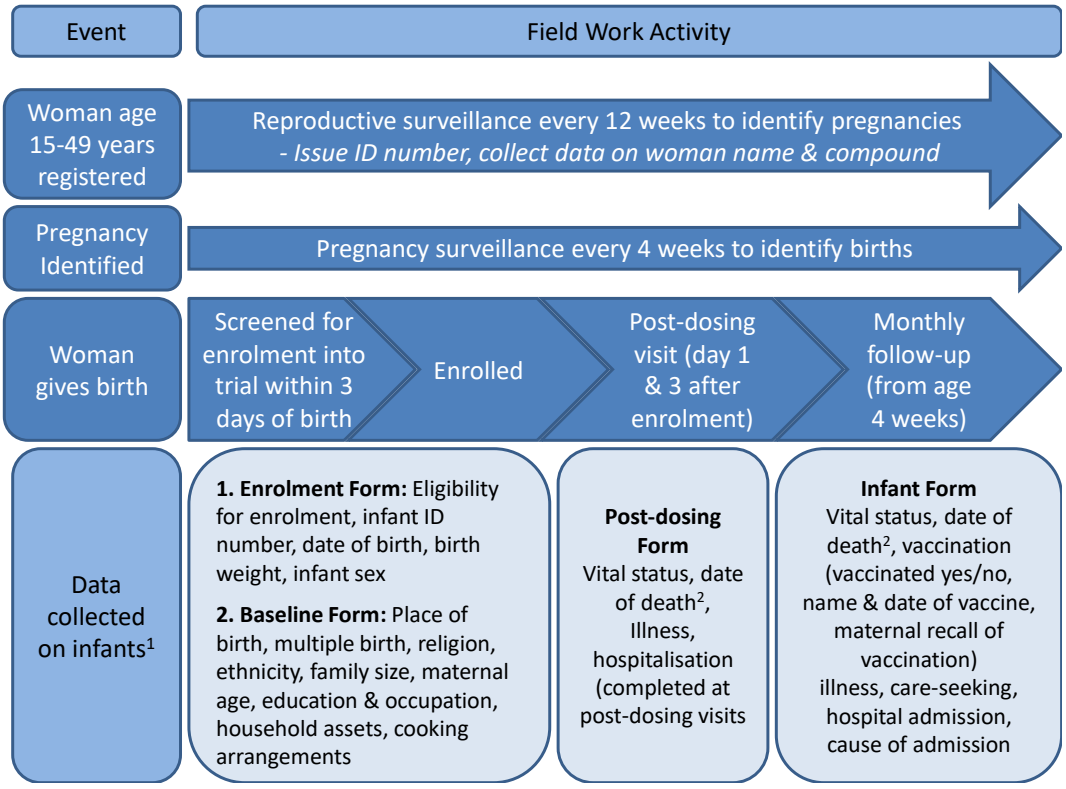
All field staff were educated to at least high-school level, and received extensive training in the Neovita study procedures and were fluent Twi speakers. I helped to train the field workers in the study procedures, both at the start of the trial, and at periodic refresher trainings until the end of fieldwork. I also directly supervised the work of the fieldworkers, through a process of direct observation and real-time feedback, in the field.

2.8. DATA COLLECTION

2.8.1. Neovita data collection processes

All data were collected on standardised paper questionnaires (**Annex 2**) and were linked using the unique identification numbers assigned to either the mother or the infant. The schedule and process for the collection of data are summarised (**Figure 2.8, Table 2.5**).

Figure 2.8: Overview of fieldwork and data collection procedures for Neovita.



1. Enrolment & baseline form completed at enrolment; postdosing form completed at the postdosing visit between 1 & 6 days of age, depending on age at enrolment; infant form completed at monthly follow up visits from 4 weeks of age until vital status at 1 year of age established
2. Date of death verified at verbal post-mortem, conducted for all infants who died

An enrolment and baseline form were completed for all infants who were screened for inclusion in the study. For those who were enrolled and supplemented, a post-dosing form was completed at both days one and three after supplementation (between one and six days of age, depending on the age at enrolment). An infant form was completed for each enrolled infant at four weekly follow-up visits until vital status at 52 weeks of age was determined (**Figure 2.8**). In addition, a verbal post-mortem (VPM) form was completed for all enrolled infants who died.

Table 2.5: Overview of data collection processes for the Neovita trial.

Visit	Frequency	Target Population	Purpose	Data collected	Associated forms
Reproductive surveillance	Every 12 weeks	All women aged 15-45 residing in the study area	Identify women of reproductive age to register in surveillance Enumeration of compounds Locate women who have moved to a different compound & assign them to the new compound Identify women who have left the study area or who have newly entered the study area	Names Women ID numbers Compound numbers	Moves form Compound enumeration form
Pregnancy surveillance	Every four weeks, and then daily in the final month of pregnancy	All pregnant women aged 15-45 residing in the study area	Identify new pregnancies Monitor outcomes of pregnancies Identify new deliveries	Details of pregnant women End dates of pregnancies Details of newly delivered women	Pregnancy form
Enrolment	Following an infant delivery	All women in the study area who have given birth	Document outcomes of pregnancies Screen infants for inclusion in Neovita Enrol infants in Neovita Collect data on all infants born in the study area	Outcomes of pregnancies Details of mothers who have delivered and newly delivered infants Infant ID numbers Infant status Infant birth weight Infant, maternal and household characteristics	Enrolment form Baseline form

Continued…..

Table 2.5 continued

Visit	Frequency	Target Population	Purpose	Data collected	Associated forms
Post-dosing visit	Days 1 and 3 post-dosing	Infants enrolled in Neovita	Document vital status of infant Monitor adverse events	Infant status & location illnesses & any adverse events	Post-dosing form
Infant follow-up visit	Every 4 weeks from four weeks of age until vital status at 52 weeks of age ascertained	Infants enrolled in Neovita	Document vital status of infant Collect data on care seeking, hospitalisations and vaccinations in the previous month	Infant status & location Care seeking, hospitalisations and vaccinations	Infant form
Infant verbal post mortem	Following the death of an infant	All Neovita infants who died	To allow a cause of death to be assigned*	Signs, symptoms and circumstances surrounding the death of an infant	Verbal post-mortem form

** Cause of death data were not available at the time of the conduct of this PhD*

2.8.2. Data collected as part of the Neovita trial

This section gives a brief description of the data collected for the Neovita trial that were subsequently used in the PhD analyses. Further details on how these data were managed, transformed, coded, and used for the PhD analyses are given in **Chapter 3**.

2.8.2.1. Birth weight data

Data on birth weight were collected by the dosing supervisors, who received weight standardisation training using a standardised protocol devised by the WHO[19]. They weighed the infants at enrolment using either electronic or spring scales (calibrated every four weeks).

Figure 2.9: Weighing an infant in a compound

The electronic scales could record birth weights to the nearest 0.1kg and the spring scales to the nearest 0.2kg. Infants were weighed between zero and 87 hours after delivery; 73% (16434) were weighed within 24 hours of delivery; 0.2% (5) were weighed more than 72 hours after delivery.

2.8.2.2. Vaccination data

The process for the recording of vaccination data during routine vaccination is described (**Section 2.3**). For the trial, at each monthly follow-up visit, caretakers (usually the mother) were asked if the infant had been vaccinated since the last visit. If they answered yes, they were asked to detail what type of vaccination the infant received (specifically whether they received oral medicine given by mouth, an injection into the leg, or an injection into the arm). The field worker asked them to recall the name of the vaccine and specifically asked if the infant had received BCG, polio, DTP, measles or yellow fever vaccination. The field worker did not ask the caretaker to specify which dose of polio or DTP was given. The field worker then undertook a visual inspection of the infant's arms to identify whether there was a BCG scar, and asked for the infant's written vaccination record. All possible sources of written information on vaccination (hereafter known as the vaccination card) were checked. Data collected on vaccination at each follow-up visit were transcribed onto the infant form (**Annex 2)**.

In the event that we did not have up-to-date vaccination data for infants who died, their families were revisited to collect and verify this information. We had incomplete vaccination data for 232 (32%) of the 715 Neovita enrolled infants who died. Caretakers of 176 (76%) of these 232 infants were interviewed to collect additional information on their infant's vaccination status prior to death. Of these 176 infants, 136 (77%) were reported to have received vaccines before death. For these 136, a vaccination card was available for 59 (43%) of infants. This increased the completeness of vaccination data for infants who died from 68% (483/715) to 76% (542/715). Those who did not have a vaccination card reported that the card had been lost or thrown away.

2.8.2.3. Mortality and morbidity data

Data on vital status and the date of death for infants who died were collected at post-dosing and infant follow-up (**Post-dosing and Infant Forms, Annex 2**). For those infants who died, the date of death was verified at the time of the VPM (**VPM Form, Annex 2**).

Data on illness, care seeking and cause-specific facility admissions were collected during the monthly infant follow-up visits (**Infant Form, Annex 2**). Mothers were asked if their infant had been ill since the previous visit and the number of illnesses the infant had. For up to two episodes of illness, data were collected on i) the start and end dates of the illness; ii) whether the illness was ongoing at the time of the visit; iii) whether care was sought outside the home for the illness and iv) if the infant was admitted to stay overnight for at least one night in a health facility. For infants who were admitted to a facility, fieldworkers documented the number of facilities where they were admitted, their associated facility codes, and for each admission, the following causes of admission: acute lower respiratory tract infection (ALRI), diarrhoea, fever / malaria and other specified causes. The causes of illness that did not result in an admission were not collected.

When mothers did not know the date the illness started, the date was coded as 08080808 (unknown). When mothers did not know the date the illness ended, or if the illness was ongoing at the time of the interview, the date was also coded as 08080808.

2.8.2.4. Illness, care seeking and medical treatment during fatal illnesses

A VPM (**Annex 2**) was conducted for infants who died, to collect data on the illness that led to their death, to assign a cause of death. Data were collected on the onset and duration of illness, on whether care was sought for the illness, when and where care was sought, and the place of death. For infants who were admitted to a health facility, data were collected on any medical therapy they received. Cause of death data were not available at the time of this PhD.

2.8.2.5. Other data collected

Data on the village and compound of residence of the mother were collected at registration in reproductive surveillance and were updated every time she moved compound. Data on additional factors such as infant and maternal characteristics, household assets and other household characteristics were collected at enrolment (**Table 2.6 and Enrolment and Baseline Forms, Annex 2**). The data collected on maternal and household characteristics are described in **Table 2.6**, along with the associated variables derived from these data. The process for deriving these additional variables is described in **Chapter 3**.

Table 2.6: Summary of source variables on infant, maternal and household characteristics, collected at enrolment, and any associated derived variables.

Source Variable	Coding / Categories	Data Form	Derived Variable
Infant Factors			
Infant Sex	Female Male	Enrolment	n/a
Number of babies born	Single Birth Twins Triplets	Baseline	*Multiple birth* Yes No
Place of delivery	Compound Facility Other	Baseline	*Facility birth* Yes No
Maternal Factors			
Number of living children, excluding current child	Continuous variable	Baseline	*No. children in family* *0-1* *2-3* *4 or more*
Age-group	15-19 years 20-24 years 25-29 years 30-34 years 35-39 years 40-44 years 45-49 years Not known	Baseline	Maternal age (years) *15 – 19* *20 – 24* *25 – 29* *30 – 34* *35 years and over*
Occupation	Government employee Private employee Self-employed Farming only Does not work Other	Baseline	*Maternal occupation* *Government/Private/Other* *Self-employed* *Farming* *Does not work*
Highest education level	None Primary school Middle, continuation school, JSS Technical, commercial, SSS, Secondary school Post-middle college, secretarial Post-secondary, nursing, polytechnic University Not known	Baseline	*Maternal Education* *None* *Primary school* *Post-primary / tertiary*

Continues….

Table 2.6 continued

Source Variable	Coding / Categories	Data Form	Derived Variable
Household characteristics			
Religion of head of household	Christian Muslim None Traditional African Other	Baseline	*Religion* *Christian* *Muslim* *Other*
Ethnic group	Akan (Bono, Ashanti, Fanti etc.) Bimoda, Chokosi Dagarti, Frafra, Kusasi Fulani Ga, Adangbe, Ewe Gonja, Dagomba, Mamprusi Konkomba, Basare Mo Sisala, Wala Zambraba Banda / Pantra Other	Baseline	*Ethnicity* *Akan* *Other*
Fuel used for cooking	Electricity LPG / Natural Gas Kerosene Coal / Lignite Charcoal Wood Straw / shrub / grass Agricultural crop waste Dung cakes Biogas, Other	Baseline	*Exposure to Indoor Smoke* *No* *Yes*
Where food is cooked	Inside Outside Other	Baseline	*Exposure to Indoor Smoke* *No* *Yes*
Main source of drinking water	Piped water Public tab Hand pump or closed borehole Open well Closed well Tanker truck Small cart with tank Surface water (river/dam/lake/pond/stream/canal/irrigation channel) Bottled Water Rain water Other	Baseline	*Socioeconomic status* *1 (poorest)* *2* *3* *4* *5 (richest)*

Continues….

Table 2.6 continued

Source Variable	Coding / Categories	Data Form	Derived Variable
Household Assets			
Toilet facility	Flush or pour toilet Pit latrine Dry toilet Bucket latrine No facility / uses open spaces or filed Other	Baseline	*Socioeconomic status* *1 (poorest)* *2* *3* *4* *5 (richest)*
Household ownership	Sole ownership Joint ownership Renting Family / relative's house House provided rent free Perching Other	Baseline	*Socioeconomic status* *1 (poorest)* *2* *3* *4* *5 (richest)*
Ownership of land	Yes / No	Baseline	*Socioeconomic status* *1 (poorest)* *2* *3* *4* *5 (richest)*
Presence of specific household assets	Electricity Chickens Sheep Other animals Mattress Stove or cooker Chair Cot or bed Divider Table Electric fan Radio or transistor Television Sewing machine Mobile telephone Mosquito net Computer Refrigerator Watch or clock Bicycle Motorcycle or scooter Animal drawn cart Car Thresher Tractor	Baseline	*Socioeconomic status* *1 (poorest)* *2* *3* *4* *5 (richest)*

2.9: DATA MANAGEMENT

2.9.1: Quality control and data processing

All paper forms were reviewed by the fieldworkers, supervisors and coordinators and any identified errors were corrected prior to submission from the field for data entry.

Data were processed at the KHRC using the SQL Server data management system (Microsoft® SQL Server™ 2008 Windows®). I contributed to the design of some of the data tables. All data were double entered. A series of automated verification, range and consistency (R&C) checks and inter-database (IDB) checks was performed weekly. I contributed to designing the R&C and IDB checks. I reviewed all queries generated from these checks and I either resolved these immediately, or I sent them as queries to the field to be resolved. I supervised all changes to the database. All changes to the data were documented using an electronic audit trail and were also marked on the original forms.

I conducted additional checks for infants who had vaccination dates which were inconsistently reported at successive follow-up visits, or when dates were consistently out of range (for instance if the date was before the infant was born, or later than the date of visit) or unknown at successive follow-up visits. These checks included requesting that the field-workers revisit the infant to re-check and verify the vaccination cards, and to take photocopies of the written record of vaccination. I reviewed these photocopies and I made the final decision about the corrections to the vaccination data.

2.9.2: Data Security and Protection

All electronic data were stored on secure password protected computers at LSHTM and KHRC. All paper forms were stored in a secure archive at KHRC. Only authorised members of the study team had access to the data.

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CHAPTER 3: ADDITIONAL METHODOLOGY FOR THE PHD

Preamble

This chapter presents the methodology specific to the PhD, including the use, generation and coding of variables used in the different analyses, and an overview of the design and methodology for the different analyses. I also describe the ethics and funding for the trial and for this PhD.

3.1. MANAGEMENT OF MISSING ILLNESS DATES.

A large proportion of illness dates were unknown (**Table 3.1**). Start dates were unknown for 43% of all illnesses (26386/61083). Among those with unknown start dates, only 1833 (3% of all illness episodes) had a known end date. A further 24553 (40% of all illness episodes) were missing both the start and end dates.

As a secondary outcome of the Neovita trial was admissions to hospital in the first year of life, a process for the assignment and imputation of illness dates resulting in an admission was devised by the senior trial management team, and implemented for the main Neovita trial analysis. I was a member of the trial management team and actively contributed to the development of this process. Dates on up to two episodes of illness were assigned for each infant.

We assigned illness dates as follows:

1. For infants who were ill and admitted to hospital at delivery, the illness start date was the date of birth

2. For infants whose illness start date was unknown and whose illness end date was known, five days (the median duration of illness among infants with known start and end dates) was subtracted from the end date, to impute the start date.

3. For infants for whom both the start and end dates were unknown, a start date of illness was imputed using the midpoint between the date the illness was reported and the date of the previous infant visit.

A total of 6% (1585) of unknown illness start dates were imputed in this way for the main trial analysis. I imputed the outstanding 94% of unknown illness start dates using the same algorithm as for the main trial analysis (**Table 3.1**).

Table 3.1: Completeness of the illness data.

Morbidity Data	Summary Statistics
A. Total illnesses	61083
B. Total missing start date of illness	26386 (43%)
C. Unknown start date, known end date	1833 (3%)
D. Missing both start and end date of illness	24553 (40%)
E. Missing start date, date imputed for main trial analysis	1585 (3%)
F. Outstanding missing start dates following imputation for main trial analysis	24801
G. Of F, those also missing end date of illness	23111 (38% of all illnesses)

3.1.1. Review of imputed dates

I assessed the imputed dates for the potential to introduce bias and for potential misclassification by reviewing their distribution by birth weight, and by time-period (**Table 3.2**).

Table 3.2: Distribution of imputed illness dates by time-period, birth weight and process of imputation

Time-period	Birth Weight	Total illness dates[1]	Date known	Missing illness start date, imputed from illness end date – 5 days	Missing both illness start and end dates, Imputed from interval between visit illness reported & previous visit	Observations for which outcome could be misclassified by time-period[2]
Neonatal	NLBW	2359	1552 (65.8)	6 (0.3)	801 (34.0)	801 (34.0)
	LBW	565	393 (69.6)	1 (0.2)	172 (30.4)	172 (30.4)
	Total	2924	1945 (66.5)	7 (0.2)	973 (33.3)	973 (33.3)
Early Infant	NLBW	15246	7914 (51.9)	408 (2.7)	6924 (45.4)	1827 (12.0)
	LBW	2740	1384 (50.5)	89 (3.2)	1267 (46.2)	338 (12.3)
	Total	17986	9298 (51.7)	497 (2.8)	8191 (45.5)	2165 (12.0)
Late Infant	NLBW	30510	17807 (58.4)	984 (3.2)	11719 (38.4)	1745 (5.7)
	LBW	5367	3012 (56.1)	197 (3.7)	2158 (40.2)	302 (5.6)
	Total	35877	20819 (58.0)	1188 (3.3)	13877 (38.7)	2047 (5.7)

1. *Excludes illnesses which occurred at >365 days of age & duplicate illnesses (illnesses having same start dates)*
2. *For neonatal period, misclassification refers to observations for which illness was imputed as neonatal, but was reported in early infant period (as a % of all neonatal illnesses), and similarly for the early and late infant periods, with observations in the late infant period being reported at >1 year of age*

The proportion of imputed dates was lowest in the neonatal and highest in the early infant periods. There was little difference in the proportion of imputed dates among LBW compared to NLBW in each time-period. The proportion of illnesses which could have

potentially been misclassified to the wrong time-period (as they were reported in a later time-period) was also similar by birth weight, and with the exception of the neonatal period (33%), the proportion was relatively small (12% in the early infant period, and 6% in the late infant period). The large number of neonatal illnesses reported in the early infant period reflects the fact that infant follow-up, which was the main source of data on infant illness, did not start until the early infant period. For those missing both start and end dates, 79% of episodes were reported within 30 days of a previous infant visit, 17% were reported between 31-60 days following the previous visit, and 3% were reported at >60 days following a previous visit. The median interval between the date of reporting of the illness and the previous visit was 25 days (IQR=8).

3.1.2. Multiple admissions for single episodes of illnesses

I assigned a 28-day window to identify admissions for related causes that could potentially be attributed to a single episode of illness. This approach has been used elsewhere[1]. These illnesses were then reviewed by Professor Karen Edmond (Consultant Paediatrician and Principal Investigator for Neovita), for review. When recommended by her, I recoded these into a single illness. In this way, in 245 instances where two admissions were reported within 28 days of each other, I classified them as a single illness.

3.2. CODING OF CAUSE SPECIFIC ADMISSIONS

Maternal report of cause of illness is known to have low specificity, therefore the potential for misclassification is high[2]. Given this, I grouped the data on cause specific admissions (ALRI, Diarrhoea, Fever/Malaria, Injury, Other) collected during the monthly follow-up visits into three broad categories: infection, non-infection and unspecified other (for other illnesses). I categorised ALRI, diarrhoea, and fever / malaria as infections. I categorised injury as non-infection.

Mothers independently reported additional symptom data at follow-up in a separate category entitled other. I extracted these data and sent them to Professor Edmond for review. Under her direction, I grouped these miscellaneous symptoms into a series of intermediate categories recommended by her (entitled corresponding broad cause in **Table 3.3**), and then into to the final broad categories of infection, non-infection and other. The re-categorisation of these is detailed (**Table 3.3**).

Table 3.3: Cause specific admissions

Other documented at follow-up	Total reports	Corresponding Broad Cause	Category for analysis
EAR	9	Infection	Infection
EYE	59	Infection	Infection
LRTI	15	Infection	Infection
Malaria	65	Infection	Infection
MEASLES	1	Infection	Infection
SEPSIS	281	Infection	Infection
SKIN PROBLEM	207	Infection	Infection
SWELL	16	Infection	Infection
SWOLLEN TESTICLES	4	Infection	Infection
TETANUS	1	Infection	Infection
UNSPECIFIED FEVER	7	Infection	Infection
URINARY INFECTION	3	Infection	Infection
URTI	87	infection	Infection
YELLOW FEVER	1	Infection	Infection
ANAEMIA	34	Blood problem	Non Infection
BLEEDING	20	Blood problem	Non Infection
JAUNDICE	67	Blood problem	Non Infection
LEUCOPAENIA	1	Blood problem	Non Infection
CARDIAC	1	Cardiac problem	Non Infection
ABDOMINAL DISTENSION	8	Gastroenterological Problem	Non Infection
FEEDING PROBLEM	22	Gastroenterological Problem	Non Infection
UNSPECIFIED ABDOMINAL PAIN	97	Gastroenterological Problem	Non Infection
VOMIT	359	Gastroenterological Problem	Non Infection
BROAD NEUROLOGICAL	109	neurological problem	Non Infection
CONVULSION	100	neurological problem	Non Infection
NERVE PALSY	1	neurological problem	Non Infection
BREATHING PROBLEM	44	Non Infection	Non Infection
OTHER NON-INFECTION	51	Non Infection	Non Infection
ASPHYXIA	25	Other problem specified cause	Non Infection
BIRTH DEFECT	24	Other problem specified cause	Non Infection
CIRCUMCISION COMPLICATION	2	Other problem specified cause	Non Infection
CONSTIPATION	17	Other problem specified cause	Non Infection
CORD PROBLEM	1	Other problem specified cause	Non Infection
EYE PROBLEM / NON INFECTION	46	Other problem specified cause	Non Infection
HEADACHE	12	Other problem specified cause	Non Infection
HERNIA	17	Other problem specified cause	Non Infection
IRRITABILITY	5	Other problem specified cause	Non Infection
LBW/PREMATURITY	79	Other problem specified cause	Non Infection
URINARY PROBLEM	12	Other problem specified cause	Non Infection
UNSPECIFIED OTHER	67	Unspecified other problem	Unknown Other

3.3. VACCINATION STATUS

I defined infants according to their vaccination status as follows:

1. *Vaccination card seen, vaccinated, date known* – if there was a legible, plausible and consistent date documented on the vaccination card (including all possible sources of written information on vaccination as described in **Section 2.8.2**).

2. *Vaccination card seen, vaccinated, date unknown* – if the infant was reported as vaccinated, but the date was either illegible, conflicting over time, or implausible (for instance if it predated the date of birth, was much earlier than the scheduled date (for instance DTP1 given in the first week of life), or later than the date of visit during which vaccination was first reported).

3. *Vaccination card seen, known not vaccinated* – If there was no evidence on the card that the infant had been vaccinated

4. *Vaccination card not seen, known not vaccinated* – this categorisation only applied if the infant's caretaker consistently reported that the infant was not vaccinated at all visits and if the card was never viewed at any follow-up visit.

5. *Vaccination status unknown*

Infants were categorised as status unknown if a) they were never seen at follow-up and if there was no information at all on their vaccination status (including all infants who died in the neonatal period and who were never seen in follow-up (which started at 4 weeks of age); b) they were seen at follow up, but the card was never seen, and their mother reported that they had been vaccinated (and the vaccine was not specified).

The choice to include an additional category for non-vaccinated infants (Category 4, infants whose vaccination card was never seen, and who were consistently reported as never having been vaccinated) was taken to maximise the retention in the analyses of infants who never attended child health clinics or vaccination clinics, and who, as a consequence may never have been issued a vaccination card. If I had relied solely on written record of vaccination to assign vaccination status, I would automatically have excluded these infants; however, these were the very infants that I was interested in for my analysis. As shown in **Section 5.6, Table 5.9**, the numbers in this category were very small (<1% for all vaccines), and so they were unlikely to have greatly impacted on the effect estimates in the various associated analyses. In order to verify their potential to bias the estimates, for certain

analyses, I undertook additional sensitivity analyses (described in **Chapter 5**), whereby I also excluded these infants.

For certain analyses, I additionally categorised infants with incomplete follow-up data as vaccination status unknown. This will be further explained in **Chapter 5**.

3.4. OUTCOME VARIABLES

The Neovita data were used to define a number of outcomes for the analyses conducted for this PhD, including uptake of vaccination services (neonatal & postneonatal vaccination and uptake of opportunities for vaccination), mortality, illness, care seeking for illness, and health facility admissions. The outcomes are defined in **Section 3.8** and in the associated papers (**Chapters 4 to 7**).

3.5. SELECTION AND DEFINITION OF EXPLANATORY VARIABLES FOR INCLUSION IN THE PHD ANALYSES

As outlined in **Section 1.10,** I sought in this PHD to investigate the association between birth weight and a number of child health outcomes The effects of additional determinants were also investigated for some of the analyses conducted in the PhD.

Table 3.4 lists the explanatory variables included in specific analyses for this PhD.

Table 3.4: Variables used in the PhD

Factors	Variables	Associated analyses
Infant	Birth Weight	All
	Infant sex	All
	Multiple birth	All
	Season due vaccine	Uptake of vaccination (**Chapters 5 & 6**)
	Illness	Uptake of vaccination (**Chapters 5 & 6**)
Maternal	Maternal occupation	All
	Maternal education	All
	Maternal age	All
	Maternal illness in the year before delivery	All
Household	Ethnicity	All
	Religion	All
	Exposure to indoor smoke	Mortality, illness & care seeking (**Chapter 4**)
	Distance to nearest health facility	All
	Number of living children in family	All
	Socioeconomic status	All

Sections 3.6 and 3.7 describe how these explanatory variables were defined and generated from the underlying Neovita data. **Section 3.8.3** describes their use in the models developed for the PhD analyses and the general approach to model building.

3.6. GENERATION OF ADDITIONAL VARIABLES FOR THE PHD ANALYSES

1. *Birth weight*

I grouped the continuous birth weight data into four standard[3-5] categories of birth weight (≥2.5kg (NLBW), 2.00-2.49kg, 1.50-1.99kg (MLBW), <1.50kg (VLBW)).

2. *Socioeconomic status*

As outlined in **Chapter 1**, household wealth and income are recognised as important distal determinants of child health[6-8], and of access to vaccination and other health services in low income settings[9-11], including in our study area[12]. Consequently, it was important for me to adjust for these effects in my analyses.

SES has been defined as comprising social class and position[13]. Position is influenced by multiple factors including ownership of assets, income and consumption. It includes different aspects of economic and social wellbeing, which allows the distinction of people across different social classes[13].

A number of indicators of SES have been developed, including occupational class, education, household income, crowding, household consumption expenditure, and ownership of assets[14,15]. There is no single best indicator of SES. Each indicator will capture a particular aspect of socioeconomic inequality, and many indicators are correlated with each other[15].

Wealth and income are difficult to quantify, especially in populations where income is frequently not derived from wages, and where few people save money[13]. As a pragmatic response to the absence of a readily available indicator of SES in low income settings, the World Bank developed an asset based index[9], generated from DHS data on household ownership of fixed assets, through a process known as principal components analysis (PCA)[9]. The DHS does not collect data on income or expenditure, but does collect data on durable assets, housing characteristics and access to utilities and services which may directly influence health[16]. The asset index measures household level SES and it reflects

material living standards[16], and it is resilient to economic shocks and to variations in income and expenditure[16,17].

PCA is a multivariable statistical technique that allows several variables in a dataset to be transformed into a smaller number of components, where each component is a linear weighted combination of the initial variables[18]. Components are ordered so that the first component explains the largest amount of variation in the original data. The second component explains additional but less variation, and so on down through the additional components[18]. Components which are more unequally distributed are given greater weight than those which are more common across all households[18].

The asset index is now used widely in low-income settings, and it was the method used for measuring SES in the Neovita trial. Its widespread use in health research in Africa facilitates comparative research. For these two reasons, I used the same approach to measure SES for my PhD.

Two main issues are observed with PCA: clumping of households into a small number of distinct clusters, and truncation, whereby the index although more evenly distributed, is spread over a narrow range, making it difficult to differentiate between different groups. These issues are best addressed by adding more variables to the analysis, and by using variables related to a variety of determinants of socioeconomic status, such as ownership of durable assets, access to utilities, and other variables that capture inequality among households[18].

Asset indices are more strongly influenced by community level infrastructure than consumption expenditure, and so are prone to an urban bias[16]. Those living in urban areas may reside in houses constructed of better quality materials, and they often have better access to water and sanitation infrastructure, and to utilities such as electricity. This may lead to misclassification of poor households in urban areas as wealthy, and wealthy households in rural areas as poor[16]. Again, inclusion of a wide variety of indicators helps to minimise this problem[16].

I used a programme provided by Lisa Hurt (member of the Neovita trial management team) to convert the data collected on household assets into an asset index[18]. A total of 44 indicators were included in the model (**Table 2.6**), covering ownership of durable assets, home and land ownership and access to utilities. In this model, ownership of land was ordered first to explain the largest variation in the data. The resulting asset index was then

categorised into quintiles of SES, with category 1 representing the poorest and category 5 the richest quintile of the population.

In order to assess how reliably the PCA derived index reflected SES in our study population, I reviewed the distribution of other key indicators of SES (education, occupation and distance to the nearest health facility) across the quintiles of SES derived from the PCA analysis (**Table 3.5**).

Table 3.5: Distribution of other indicators of socioeconomic status by quintile of socioeconomic status as derived by PCA

Other indicator of socioeconomic status n (% of total in category)	**Quintile of socioeconomic status**				
	1 (Poorest)	**2**	**3**	**4**	**5 (Richest)**
Maternal education - none	2723 (60)	1763 (39)	1185 (26)	953 (21)	503 (11)
Maternal education – secondary / tertiary	66 (2)	164 (4)	270 (6)	452 (10)	1330 (29)
Maternal occupation - farmer	2757 (61)	1946 (43)	1276 (28)	559 (12)	133 (3)
Maternal occupation - government employee	56 (1)	122 (3)	162 (4)	251 (5)	634 (14)
Distance to health facility >5km	1778 (39)	1113 (25)	593 (13)	252 (5)	66 (1)
Place of delivery – Non-facility	2425 (54)	1420 (31)	900 (20)	469 (10)	160 (3)

There was good agreement between the classification of infants by SES and these other indicators. For instance, a higher proportion of infants who were in the poorest category of SES were born to mothers with no education, who were farmers, who lived more than 5km from a health facility, and who did not give birth in a health facility. This demonstrates consistency in the categorisation of infants by SES and by these other indicators of low SES.

3. Exposure to indoor smoke

I used the data on household cooking facilities to categorise households according to their exposure to solid fuel indoor smoke. I defined exposure to indoor smoke as cooking indoors using coal, lignite, charcoal, wood, straw, shrubs, grass, agricultural crop waste, dung cakes or other types of fuel, versus either cooking outdoors or cooking indoors with electricity, natural gas, biogas or kerosene, in accordance with a definition previously used by the WHO[19].

4. Distance to health facility

Each infant enrolled in the trial had an assigned compound number. Every time the infant moved compound, the compound number was updated. Each compound number was

comprised of a three-letter village code and a four-digit number. Each village code corresponded to a defined geographical unit in our study area. These codes were used to categorise infants by their distance to the nearest health facility.

Robin Nesbitt from the University of Heidelberg kindly provided data on distance to the nearest health facility. She calculated distance by generating Euclidean (straight-line) distances between village centroids and health facilities, using methods described in detail elsewhere[20]. Briefly, GPS coordinates of the health facilities in the study area, of 433 village centroids and of 47537 compounds in 173 larger villages were taken as part of demographic surveillance for previous field trials conducted in the study area. These co-ordinates were then translated into straight-line distances using ArcMap version 10.0. I assigned these distances to the corresponding village code for each infant. I then assigned the infants to three categories of distance (<1km, 1-5km, >5km).

For analyses relating to vaccine uptake and timing, I used the distance at the time the vaccine was scheduled to be given. For all other outcomes, I used the distance at the time the outcome was measured. For example, for analyses relating to death, I used the distance relating to the compound where the infant resided at the time of death.

5. *Season when vaccine was due*

For analyses relating to uptake and timing of vaccination, I categorised infants according to whether the specified vaccine was due in the wet or the dry season. Based on advice from colleagues at the KHRC, I defined the wet season as composing of April, May, June, July, October, and November, with all remaining months comprising the dry season.

6. *Infant illness*

For analyses relating to uptake and timing of vaccination, I categorised infants according to whether their caregivers reported that they had an illness close to the time before the vaccine was due. This was based on caregiver's report of illness since the previous visit, reported at the first visit following the due date for vaccination. Similarly, for analyses relating to uptake of opportunities for vaccination, I categorised infants according to whether their caregivers reported that they had an illness close to the time of the opportunity.

7. *Infant time-periods*

I defined a number of time-periods within infancy for use in the different analyses including: a) the neonatal period (0 to 27 days or 0 to 3 completed weeks of age (weeks 0,

1, 2 and 3)); b) the postneonatal period (28 to 364 days or 4 to 51 completed weeks of age); c) the early infant period (28 to 182 days or 4 to 25 completed weeks of age); d) the late infant period (183 to 364 days or 26 to 51 completed weeks of age); and e) the infant period (0 to 364 days or 0 to 51 completed weeks of age).

3.7. RECODING OF VARIABLES

Some of the infant, maternal and household variables collected for the Neovita trial comprised data with many categories, and the number of infants within some of these categories was very small. To avoid problems with small numbers in my analyses, I generated new variables with fewer categories for these factors. The re-categorised variables are described in **Table 2.6**.

3.8. OVERVIEW OF PHD ANALYSES

In order to meet the overall objectives of the PhD, I conducted a series of analyses, the results of which are presented in **Chapters 4 to 7** as a series of papers. In this section, I present a brief overview of these analyses. I discuss in detail the specific methodological considerations associated with each analysis in the corresponding results chapters.

I describe in greater detail my general approach to model building in **Section 3.8.3**.

3.8.1. Study population for each analysis

The process for recruitment and enrolment of infants in Neovita is described in **Sections 2.6 and 2.7 and in Figure 2.8**. All infants enrolled in Neovita were eligible for inclusion in the analyses. Infants were excluded from each analysis if they had incomplete data on any of the explanatory variables included in the analyses for that paper, or if they were missing data on the outcome. Additional inclusion and exclusion criteria for each of the analyses are summarised individually in each associated paper.

3.8.2. Analytical approach

The specific objectives and outcomes for each paper are summarised in **Table 3.6**. For all analyses, I conducted a univariable analysis of the association between each explanatory variable and the outcome. In order to explore how the association between birth weight and the outcome (the primary association) was affected by the other explanatory variables, I first constructed two by two tables of the primary association, stratified in turn by each of the other explanatory variables. I then conducted a bivariable analysis of this association,

adjusted in turn for each of the other explanatory variables. I conducted a preliminary assessment of confounding between birth weight and the other explanatory variables by examining how the estimate of the association between birth weight and the outcome changed when adjusted for the other explanatory variable. For all papers, I fit a causal model to assess the association with birth weight and other determinants and the outcome of interest. I adjusted for all possible confounders (selected a priori based on the known determinants of these outcomes (detailed in **Chapter 1**), as described in **Table 3.4**.

Table 3.6: Summary of the methodology for each PhD paper

Paper	Specific objectives of the paper	Methods	Outcome measures
Paper 1: Declining birth weight as a risk factor for mortality, illness, care seeking and admissions during infancy in Ghana	1) To generate estimates of the association between birth weight, and i) mortality and ii) illness, and among those reporting illness, estimates of the association between birth weight and iii) care seeking, and iv) health facility admissions in the first year of life. 2) To assess how these estimates vary between the neonatal, early and late-infant periods 3) To assess whether the association between birth weight and mortality varies by distance to the nearest health facility, and by SES.	Kaplan Meier curves of probability of survival Cox regression, random effects Poisson regression, random effects logistic regression	1) Mortality hazard ratios 2) Illness rate ratios 3) Care seeking odds ratios 4) Admission odds ratios
Paper 2: Delayed Vaccination of Low Birth Weight Infants in Rural Ghana: Results from a Population-based Prospective Cohort Study	1) To assess whether LBW is a determinant of DTP1 and DTP3 vaccination 2) To assess whether maternal education or SES modifies the association between birth weight and vaccination with DTP1 and DTP3 3) To quantify other determinants of delayed DTP1 and DTP3 vaccination	Kaplan Meier curves of time to vaccination Poisson regression	Vaccination rate ratios for: DTP1 between a) 0-10, b) 0-14 and c) 0-18 weeks of age, And DTP3 between a) 0-18, b) 0-22 and c) 0-26 weeks of age.

Continued…..

Table 3.6 continued

Paper 3: Neonatal vaccination of LBW infants in Ghana	1) To evaluate whether birth weight is a determinant of neonatal BCG vaccination 2) To assess whether the association between birth weight and neonatal BCG vaccination varies by place of delivery and infant illness 3) To identify other determinants of neonatal BCG vaccination	Logistic regression	Odds ratios for BCG vaccination by the end of the neonatal period.
Paper 4: Missed opportunities for infant vaccination in Ghana, and the potential impact of their utilisation on vaccine uptake and timing.	1) To quantify the number and types of opportunities for vaccination, and the associated missed opportunities for vaccination in the first year of life 2) To identify the determinants of uptake of those opportunities 3) To assess how using the first opportunity for vaccination could theoretically increase the uptake of vaccines included in the routine childhood immunisation schedule.	Descriptive analyses, logistic regression, Kaplan Meier curves of the probability of vaccination	1) Primary care based and facility-based opportunities for vaccination 2) Odds ratios for taking an opportunity 3) Actual and theoretical vaccine uptake rates

3.8.3. Causal frameworks

Child health outcomes are known to be influenced and driven by a wide variety of social, economic, biological and environmental factors[21], which inter-relate in complex and sometimes poorly understood ways, through processes of mediation, effect modification and confounding. Therefore, in order to understand and estimate the effect of these risk factors, including birth weight on these outcomes, consideration of how these risk factors relate to and influence each other is required.

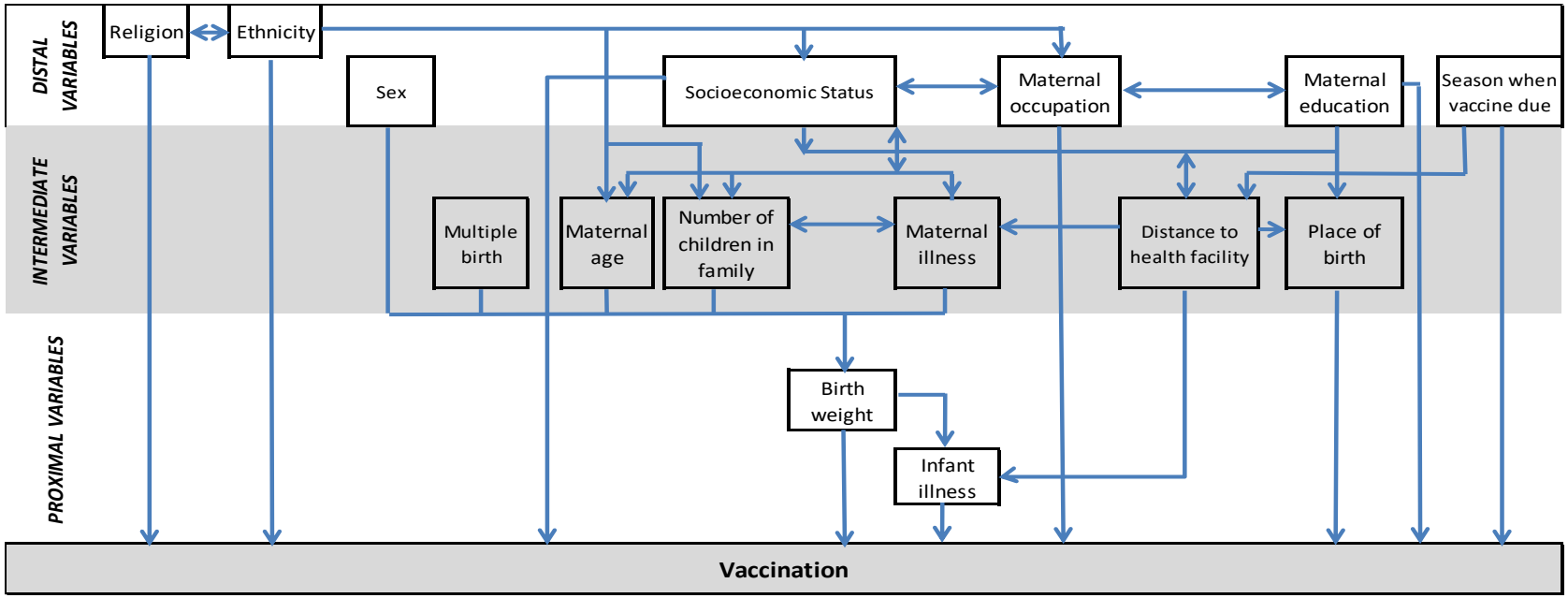
Mosley and Chen[21] proposed that these factors could be arranged and described in a hierarchical framework comprising distal socioeconomic factors, which operate through intermediate and proximal factors, which themselves influence the likelihood of the outcome. This approach provides a useful framework from which to organise and structure the analyses of these associations[22].

With this in mind, I constructed a hierarchical framework (**Figure 3.1**) of the recognised determinants of vaccination[10-12] in order to guide most of the analyses conducted for the PhD. This framework was modified slightly for specific analyses. The model was comprised of distal, intermediate and proximal variables. I hypothesized that the intermediate and proximal variables mediated the effects of the distal variables, and that the proximal variables mediated the effects of the intermediate variables. I hypothesized that illness mediated the effect of birth weight.

For the multivariable analyses, I initially constructed a model comprised of the distal determinants, I then added the intermediate determinants, and assessed how these changed the effect size of the distal determinants. I then added the proximal determinants and assessed how they changed the effect size of the intermediate and distal determinants. I finally added any mediating variables, and again assessed changes to the effect sizes. Unless otherwise indicated, I retained all explanatory variables in the final model, to adjust for all possible confounding effects.

For all models, I assessed the strength of the evidence of an association using 95%CIs and either Wald tests (for univariable analyses) or likelihood ratio tests (for multivariable analyses).

Figure 3.1: Hierarchical framework of the determinants of vaccination*



* *Mediation is indicated by arrows linking the variables across different levels.*

When indicated, I undertook additional investigations of whether the association between birth weight and the outcome was modified by other factors by fitting interaction terms (combining birth weight and the possible modifying factor) to the final model.

3.8.4. Study Power

The sample size for these analyses was determined by the number of infants enrolled in the Neovita trial. A total of 22955 infants were enrolled in Neovita, as discussed in **Section 2.6**. Based on this total number of enrolled infants, and an assumed loss to follow-up of 10%, giving an available sample of 20660 infants, I undertook power calculations for the mortality analysis (**Paper 1**) and the postneonatal vaccination analysis (**Paper 2**). Approximately 14% of infants in SSA are LBW[23], equating to 17768 NLBW infants and 2892 LBW infants in our sample. Before analysing these data, there were no available estimates on the proportion of LBW infants that were MLBW (weighing 1.50-1.99kg) and VLBW infants (weighing <1.50kg). These sample size calculations were based on two theoretical distributions of LBW (one theoretical distribution of 10% of infants weighing 2.00-2.49kg, 3% MLBW and 1% VLBW, and a second distribution of 11% of infants weighing 2.00-2.49, 2.5% MLBW and 0.5% VLBW).

3.8.4.1. Power to detect the association between birth weight and infant mortality

The infant mortality rate (IMR) in Ghana has been estimated at 41/1000 live births[24]. This power calculation was based on two different theoretical scenarios of varying mortality rates among the different categories of LBW compared to NLBW infants. In the first scenario infants weighing 2.00-2.49kg had a mortality hazard ratio (MHR) of two compared to NLBW infants, MLBW infants had a MHR of five and VLBW infants had a MHR of 15. In the second more conservative scenario, the MHRs were 1.5 for infants weighing 2.00-2.49kg, 2.5 for MLBW infants and 5 for VLBW infants.

Table 3.7 presents the power to detect these various mortality hazard ratios among the different categories of LBW infants compared to NLBW infants in the overall infant period, based on the two distributions of birth weight and on the two distributions of MHR.

Table 3.7: Power to detect the mortality hazard ratio (MHR) for different distributions of birth weight and different distributions of MHR.

		Scenario 1		Scenario 2	
	No of infants (%)	**Estimated MHR**	**Power**	**Estimated MHR**	**Power**
≥2.50kg	17768 (86%)	ref		ref	
2.00-2.49kg	2066 (10%)	2	99%	1.5	98%
1.50-1.99kg	620 (3%)	5	99%	2.5	99%
<1.50kg	206 (1%)	15	99%	5	99%
≥2.50kg	17768 (86%)	ref		ref	
2.00-2.49kg	2272 (11%)	2	99%	1.5	98%
1.50-1.99kg	517 (2.5%)	5	99%	2.5	99%
<1.50kg	103 (0.5%)	15	99%	5	99%

These calculations indicated that there was good power to detect moderate differences in mortality among the different categories of LBW compared to NLBW infants.

3.8.4.2. Power to detect the association between birth weight and DTP1 and DTP3 vaccination.

It has previously been reported in the Neovita study area[25] that the uptake for each of DTP1 and DTP3 at four weeks after the vaccination due date (10 and 18 weeks of age) was 78% and 46% respectively. I assumed that this uptake was equivalent to that of NLBW infants.

This power calculation was based on two different scenarios of varying proportions of vaccination among the different categories of LBW compared to NLBW infants. In the first scenario infants weighing 2.00-2.49kg had a 10% lower vaccine uptake at 4 weeks after the due date compared to NLBW infants. This corresponds to a vaccine uptake of 70.2% for DTP1 and 41.4% for DTP3. I assumed that for MLBW infants, the uptake was 20% lower, corresponding to a DTP1 uptake of 62.4% and a DTP3 uptake of 36.9%. For VLBW infants, I assumed vaccine uptake was 30% lower, corresponding to a DTP1 uptake of 54.6% and a DTP3 uptake of 32.3%.

The second scenario assumed that infants weighing 2.00-2.49kg had a vaccine uptake 20% lower than that of NLBW infants (62.4% for DTP1 and 36.8% for DTP3), MLBW infants had a vaccine uptake that was 30% lower (54.6% for DTP1 and 32.2% for DTP3) and that VLBW infants had a vaccine uptake that was 40% lower (46.8% for DTP1 and 27.6% for DTP3).

Table 3.8 presents the power to detect these various differences in vaccine uptake among the different categories of LBW infants compared to NLBW infants within 4 weeks of the

vaccine due date for each of DTP1 and DTP3, based on the two distributions of birth weight and on the two distributions of vaccine uptake.

Table 3.8: Power to detect differences in vaccine uptake for different distributions of birth weight and different distributions of vaccine uptake, at 4 weeks after the due date for each of DTP1 (10 weeks of age) and DTP3 (18 weeks of age).

			DTP1 at 10 weeks of age		DTP3 at 18 weeks of age	
	No of infants (%)	**Reduction in Uptake**	**Estimated % Vaccine Uptake**	**Power**	**Estimated % Vaccine Uptake**	**Power**
≥2.50kg	17768 (86%)	Ref	78	-	46	-
2.00-2.49kg	2066 (10%	10%	70.2	99%	41.4	98%
1.50-1.99kg	620 (3%)	20%	62.4	99%	36.9	99%
<1.50kg	206 (1%)	30%	54.6	99%	32.3	98%
≥2.50kg	17768 (86%)	Ref	78	-	46	-
2.00-2.49kg	2272 (11%)	20%	62.4	99%	36.8	99%
1.50-1.99kg	517 (2.5%)	30%	54.6	99%	32.2	99%
<1.50kg	103 (0.5%)	40%	46.8	99%	27.6	97%

The results of these calculations suggested that there was good power to detect moderate differences in vaccine uptake at four weeks after the vaccine due date for each of DTP1 and DTP3.

3.8.5. Management of co-linearity

When I thought two explanatory variables might be co-linear, I undertook an assessment of co-linearity, by monitoring inflation of the log standard errors of the explanatory variables when the model of the primary association was adjusted for both possible co-linear variables, compared to when it was adjusted for them individually. Where I identified instances of co-linearity, I generated composite variables of the co-linear explanatory variables.

3.9. ETHICS

The work undertaken for this PhD was covered by the ethics approval granted for the Neovita trial. The Ethics Committees of the Ghana Health Service, the World Health Organisation (WHO), the London School of Hygiene & Tropical Medicine (LSHTM), and the Kintampo Health Research Centre (KHRC) granted ethics approval for Neovita. Neovita is registered with the Australian New Zealand Clinical Trials Registry (registration number ACTRN12610000582055).

3.10. FUNDING

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RESULTS

CHAPTER 4: LOW BIRTH WEIGHT AS A RISK FACTOR FOR MORTALITY, ILLNESS, CARE SEEKING AND ADMISSIONS

Preamble

In this chapter, I present the first of four PhD papers that have been submitted to or published in peer-reviewed journals. The paper addresses the first objective of the PhD, namely to assess whether LBW is a determinant of mortality, illness, care seeking, and health-facility admissions in the first year of life, and in each of the neonatal, early and late infant periods. ***Section 4.1*** *presents a short introduction to the paper. I present the paper itself in* ***Section 4.2****. I provide an additional explanation of the methods in* ***Section 4.3,*** *and additional results and discussion in* ***Section 4.4****.*

4.1. INTRODUCTION

As highlighted in **Chapter 1**, the overall aim of the PhD was to assess whether LBW is a marker for under-vaccination. Infants at risk of under-vaccination, including LBW infants may be more likely to contract or die from VPDs, due to their prolonged or increased risk of infection. Due to a lack of diagnostic data on VPDs in the Neovita study population, I was not able to investigate the association between an infant's vaccination status and their risk of VPDs. In the absence of this, and in order to contextualise the vaccination practices for LBW infants in relation to other important child health outcomes, I investigated the extent to which LBW infants are at increased risk of illness and death, and the extent to which they seek and receive care for illness. The study population for the analyses of illness and death were 22906 infants who were enrolled in the Neovita trial, and who had complete covariate data. The study population for the analyses of care seeking and admissions were 19292 Neovita enrolled infants, with complete covariate data, who reported illness in the first year of life. I used Cox regression to investigate the association between birth weight and mortality, and random-effects Poisson regression to investigate the association between birth weight and illness (as many infants had more than one episode of illness). I used logistic regression to investigate the association between birth weight and both absence of care seeking, and health facility admissions. All effect estimates were adjusted a priori for potential confounders.

4.2. PAPER 1: LOW BIRTH WEIGHT AS A RISK FACTOR FOR MORTALITY, ILLNESS, CARE SEEKING AND ADMISSIONS DURING INFANCY IN GHANA: A PROSPECTIVE POPULATION-BASED COHORT STUDY.

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Maureen O'Leary
Principal Supervisor	Sara Thomas
Thesis Title	Low birth weight as a risk factor for undervaccination in rural Ghana; evidence from a population based cohort

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*		Was the work subject to academic peer review?	

**If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.*

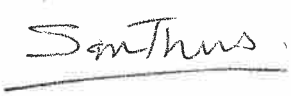
SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Bulletin of the World Health Organisation
Please list the paper's authors in the intended authorship order:	Maureen O'Leary, Karen Edmond, Sian Floyd, Sam Newton, Gyan Thomas, Sara L. Thomas.
Stage of publication	In peer review

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	The original idea for the research included in this paper was developed by me, Maureen O'Leary in collaboration with Karen Edmond. This research is based on a secondary analysis of data collected as part of a randomised control trial of neonatal vitamin A supplementation. I was the epidemiologist on the trial and I spent 3 years in Ghana overseeing and ensuring the quality of the data collected for the trial and subsequently included in this research. I prepared the datasets used in the analyses, with assistance from Karen Edmond, who advised on the coding of cause-specific admissions, and on the identification of multiple admissions for a single illness. I designed the research and developed a detailed plan of analysis, with supervision and input from Sara Thomas and Sian Floyd. In particular, Sian Floyd and Sara Thomas advised on the statistical methodology used for the analysis, and on the stratification by infant time-period. Sara Thomas also advised on the post hoc analysis of verbal post-mortem data. I wrote the program for the analyses, ran the analyses and drafted the manuscript. Sara Thomas and Karen Edmond provided advice on the interpretation of the results, in particular the limitations associated with the use of illness, care-seeking and admissions data based on maternal recall. All co-authors commented on the manuscript and I revised the manuscript accordingly. I prepared the manuscript for submission and liaised with the editorial team. The manuscript was peer-reviewed.

Student Signature:  **Date:** 27/7/16

Supervisor Signature:  **Date:** 27/7/16

Low birth weight as a risk factor for mortality, illness, care seeking and admissions during infancy in Ghana: a prospective population-based cohort study.

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Abstract

Background

We used randomised-controlled-trial data from rural Ghana to investigate the effect of birth weight on infant mortality, illness, care seeking and health-facility admissions.

Methods

We compared low birth weight (LBW) (2.00-2.49kg, 1.50-1.99kg (moderately LBW, MLBW), <1.50kg (very LBW, VLBW)) and non-LBW (NLBW, ≥2.5kg) infants. Our outcomes were 1) mortality, 2) illness, and among those with illness, 3) absence of care seeking and 4) health-facility admissions in infancy (0-364 days), and in the neonatal (0-27), early (28-182) and late (183-364) infant periods. We generated adjusted mortality hazard ratios (aHR) using Cox regression, illness rate ratios (aRR) using random-effects Poisson regression (allowing for multiple illnesses) and odds ratios (aOR) for non-care seeking and admissions using logistic regression, adjusted for infant, maternal and household factors.

Results

Among 22906 infants, those weighing 2.00-2.50kg were twice (aHR=2.13; 95%CI: 1.76-2.59); MLBW infants eight times (aHR=8.21; 95%CI:6.26-10.76), and VLBW infants 25 times (aHR=25.38; 95%CI:18.36-35.10) more likely to die in infancy. The effect varied by time-period (p-interaction <0.0001). VLBW infants had 48 times the mortality rate in the neonatal period (aHR=48.45; 95%CI:32.81-71.55), and eight times the rate in late infancy (aHR=8.42; 95%CI:3.09-22.92). Birth weight was not associated with illness overall but the association varied over time (p-interaction=0.0013). MLBW (aRR=1.57; 95%CI:1.27-1.95) and VLBW (aRR=1.58; 95%CI:1.13-2.21) infants had higher illness rates in the neonatal period. MLBW infants had an absence of care-seeking in the neonatal (aOR=3.30; 95%CI:1.98-5.48) and early (aOR=1.74; 95%CI:1.26-2.39) infant periods. We found no association with admissions overall or by time-period.

Conclusions

Strategies to minimise mortality throughout infancy and to improve care seeking are needed.

Introduction

Approximately 14% of infants in low and middle income countries are born weighing <2.5kg at birth;[1] many are preterm. Most research on mortality and illness among low birth weight (LBW) infants has focused on the neonatal period, when a disproportionate number of deaths occur[2]. Few studies[3-6] have generated population-based estimates from sub-Saharan Africa (SSA) on postneonatal outcomes, particularly for very low birth weight (VLBW) infants (born weighing <1.50kg)[7], of whom almost all are preterm[8]. Lower care seeking for sick neonates has been reported when families think they are likely to die[9]. This may be more common for fragile, small LBW infants, adversely impacting their mortality risk, and for infants with additional barriers to care seeking such as poorer infants living far from a health facility[9].

We used data from a randomised controlled trial assessing neonatal vitamin A supplementation impact on infant mortality in rural Ghana, to investigate birth weight as a risk factor for mortality and illness in infancy.

Our primary objective was to determine the extent to which LBW infants were at increased risk of mortality and illness in the first year of life. Secondary objectives were a) to assess among sick infants the association between birth weight and care seeking and health facility admissions; b) to examine how the effect of birth weight varied between the neonatal, early and late infant periods, and c) to investigate whether any effect of birth weight on mortality varied by distance to the nearest health facility or by socioeconomic status.

Methods

The Neovita study was conducted at the Kintampo Health Research Centre (KHRC) in the Brong-Ahafo region of rural Ghana. The study has been described in detail elsewhere[10,11]. The study area is served by four district hospitals and 69 health facilities. All pregnancies and deliveries among women aged 15-49 years between August 2010 and November 2011 were identified through a population-based prospective surveillance system. Newborns residing in the study area for at least six months, who were aged ≤3 days at screening, and who could suck or feed were enrolled.

Fieldworkers weighed the infants using calibrated electronic or spring scales. The electronic scales recorded weights to the nearest 0.1kg, and the spring scales to the nearest 0.2kg. Most infants (73%, 16434) were weighed within 24 hours of delivery; 0.2% (5) were weighed >72 hours after delivery.

Fieldworkers collected data from pregnant women on the date of their last menstrual period (LMP) during pregnancy surveillance and at enrolment. Data on infant, maternal and household characteristics were collected at enrolment. At monthly follow-up visits for the first year of life, field workers collected data on infant illness (with start and end dates) since the last visit, and on care seeking and facility admissions among those reporting illness. All illness-related data were based on maternal recall as data from health services and child health records were unavailable. Data were also collected on the infant's vital status, and when applicable, date of death.

Our primary outcomes were 1) mortality and 2) illness in the first year of life. For each illness, we investigated 3) absence of care seeking and 4) admissions to a health facility.

For 3% of illness episodes missing the illness start date, this date was imputed as the end date minus five days (the median duration of illness). For the 40% of illnesses missing both

start and end dates, the start date was imputed as the midpoint between the date the illness was reported and the date of the previous follow-up visit. Facility admissions occurring within 28 days of a previous admission were reviewed to assess whether they were a single ongoing illness. For two infants missing date of death (0.3% of all deceased infants), we imputed this date as the midpoint between the first report of death and the last report of the infant being alive.

The primary exposure was birth weight, in standard[7,8,12] categories (≥2.5kg (NLBW), 2.00-2.49kg, 1.50-1.99kg (moderately LBW, MLBW), <1.50kg (VLBW)).

Data on LMP were missing (57% (16398/28498)) or inconsistently reported (7% (1935/28498)) for 64% of pregnancies. Given this, and the known discordance between LMP and ultrasound in gestational age assessment[13-15], we did not investigate the association between gestational age and our outcomes.

Follow-up for all analyses started at birth and ended at a) 364 days of age for infants alive and in follow-up throughout the study; b) the date of death for infants who died before day 364 and c) the last date the infant was seen, for live infants who exited the study before day 364.

Data analysis

All analyses were conducted using STATA 13.1 (STATACORP, 2013).

We generated Kaplan-Meier curves of the probability of survival in LBW compared to NLBW infants and calculated mortality rates for the first year of life. As mortality rate changes rapidly, particularly in the early neonatal period, we used multivariable Cox regression to calculate adjusted hazard ratios for the association between birth weight and mortality.

To allow for repeated illness events, we used random effects Poisson regression to calculate adjusted rate ratios for the association between birth weight and infant illness.

Restricting the analyses to reported episodes of illness, and allowing for multiple illnesses for each infant, we used random effects logistic regression to calculate adjusted odds ratios for the association between birth weight and a) absence of care seeking, and b) admission for the illness.

For each analysis, we assessed whether the effect of birth weight varied between the neonatal (0-27 days), early (28-182 days) and late infant (183-364 days) periods, by fitting birth weight as an interaction term with time-period. Similarly, for mortality, we assessed whether the effect of birth weight varied by a) distance to the nearest health facility, or b) socioeconomic status.

For all analyses we used likelihood ratio tests and 95% confidence intervals (95%CI) to assess the statistical evidence for an association between birth weight and each outcome. In each analysis we adjusted a priori for infant (sex, multiple birth), maternal (education, age, occupation, illness), and household (religion, ethnicity, socioeconomic status, exposure to indoor smoke, distance to nearest health facility, number of children in the family) factors.

Funding and Ethics

Neovita was funded by the Bill and Melinda Gates Foundation. Ethics approval for the collection of data included in this study was granted by the Ethics Committees of the World Health Organisation (WHO), the London School of Hygiene & Tropical Medicine and the KHRC.

Results

Of the 22955 Neovita enrolled infants, we included 22906 (99.8%) with complete covariate data in the analyses, of whom almost 16% (3584) were LBW (**Table 1**). Of included LBW infants, 13% weighed between 2.00-2.49kg, approximately 2% were MLBW, and 0.5% were VLBW.

Infant mortality

Three percent (698/22906) of infants died in infancy; 277 (39.7%) of these deaths were in the neonatal period, 248 (35.5%) in early infancy, and 173 (24.8%) in late infancy. Infant mortality rates per 1000 live births were 30.5 overall, 22.4 for NLBW infants, 48.6 for 2.00-2.49kg infants, 160.0 for MLBW infants, and 402.0 for VLBW infants.

Monthly mortality declined with age but was consistently higher for LBW infants compared to NLBW infants (**Figure 1**). The smaller the baby at delivery, the more likely they were to die (p-trend<0.0001). After adjusting for all potential confounders, infants weighing 2.00-2.50kg were twice (aHR=2.13; 95%CI:1.76-2.59); MLBW infants were eight times (aHR=8.21; 95%CI:6.26-10.76), and VLBW infants 25 times (aHR=25.38; 95%CI:18.36-35.10) more likely to die than NLBW infants in the first year of life (**Table 2**).

There was strong evidence that the effect of birth weight varied over the infant period (p-interaction <0.0001) (**Table 3**). The trend of higher mortality with lower birth weight was seen in each time-period but the magnitude of the association declined over time (**Table 3**). For example, compared to NLBW infants, VLBW infants had 48 times the mortality rate in the neonatal period (aHR=48.45; 95%CI:32.81-71.55), declining to eight times the rate in the late infant period (aHR=8.42; 95%CI:3.09-22.92). Similar patterns were seen for MLBW infants (aRR=14.71 (95%CI:10.37-20.86) in the neonatal period and 1.61 (95%CI:0.59-4.39) in the late infant period) and to a lesser extent for infants weighing 2.00-2.49kg (aRR=2.29 (95%CI:1.66-3.15 versus 1.60 (95%CI:1.09-2.35)).

The effect of birth weight on mortality did not vary by either distance to the nearest health facility or socioeconomic status (p-values for interaction all > 0.2).

Infant illness

Mothers reported 56610 episodes of illness for 19292 infants. Following an initial spike in the neonatal period, age-specific illness rates increased over time (**Figure 2**). Upon adjustment for other factors, birth weight was not associated with infant illness overall (**Table 3**); although the association varied with time (p-interaction=0.0013). Compared to NLBW infants, both MLBW (aRR=1.57; 95%CI:1.27-1.95) and VLBW (aRR=1.58; 95%CI:1.13-2.21) infants had higher illness rates in the neonatal period; there was little evidence of an association later in infancy (**Table 3**).

Care seeking

There was evidence that care was less likely to be sought for LBW infants, specifically MLBW infants, in infancy (aOR for an absence of care seeking=1.46; 95%CI:1.18-1.81). On univariable analysis an association was found for VLBW infants (OR=1.76; 95%CI:1.18-2.63), but upon adjustment for infant age and other covariates this association was no longer apparent (aOR=1.05; 95%CI:0.68-1.63) (**Table 2**). Care seeking varied between the neonatal, early and late infant periods (p-interaction=0.0002), although in each period an association was only evident for MLBW infants. Absence of care seeking for MLBW infants was three times and almost twice as likely in the neonatal (aOR=3.30; 95%CI:1.98-5.48) and early infant periods (aOR=1.74; 95%CI:1.26-2.39) respectively. No association was found in the late infant period.

Admissions

A total of 4187 admissions were reported for 3485 infants. We found no association between birth weight and admissions in the first year of life (**Table 2**), nor did this association vary by time-period (p-interaction=0.1383).

Additional analyses

To further understand how illness, care seeking and admissions related to mortality, we undertook additional post-hoc exploratory analyses of VPM data for infants who died. We compared disease progression, care seeking and admissions during the fatal illness among NLBW and LBW (<2.5kg) infants using proportions and chi-square tests. (**Table 4**). Data on cause of death were unavailable.

VPM data were available for 684/698 (98%) of infants who died. Care was less likely to be sought for LBW infants than NLBW infants (77.1% compared to 87.0%; p=0.001). Of those for whom care was sought care, professional medical care (seeking care from a hospital, clinic, doctor, nurse or pharmacy) was sought for a smaller proportion of LBW infants (85.6%) than NLBW infants (93.5%) (p=0.002). There was little evidence of differences in the duration of illness, in the time to seek care, and in the proportions for whom care was sought from non-medically trained sources, who were admitted to a health facility or who died in a health facility (**Table 4**).

Discussion

LBW continues to adversely impact on infant outcomes throughout the first year of life. LBW infants, especially VLBW infants, have substantively higher mortality rates throughout infancy, with a notable trend of increasing mortality with decreasing birth weight.

Although several studies have investigated the association between mortality and LBW in SSA[5,16-21]; few have generated population-based mortality estimates for MLBW and VLBW infants. A single 20 year old study from Malawi[21] reported neonatal mortality rates 13 times higher, and infant mortality rates five times higher among infants with birth weights <2.00kg, similar to our estimates for MLBW infants. VLBW is considered a sensitive and specific marker for preterm birth[22,23]. Given this, we compared our results for VLBW infants to those of two studies[6,24] which investigated mortality among preterm and small for

gestational age (SGA) infants. Katz et al reported that infants in low and middle income countries who were both preterm and SGA were over 16, 19 and 6 times more likely to die in each of the early neonatal, late neonatal and postneonatal periods. A study from Tanzania reported that preterm SGA infants were 15 and 3 times more likely to die in each of the neonatal and postneonatal periods. Our estimates for VLBW infants in these time-periods are substantively higher.

The marked association between birth weight and mortality in our study was not reflected in corresponding associations with illness (except in the neonatal period), or facility admissions. Interestingly our data suggest lower care seeking for LBW infants, specifically for MLBW infants in the first year of life in the neonatal and early infant periods, and also during fatal illnesses.

Few studies have investigated the association between birth weight and illness in Africa, with varying results. Several studies have reported no association between birth weight and infant illness, clinic attendance or admissions[3,25-28]. In contrast, an analysis of hospital admissions (based on both written record and maternal recall) collected from a peri-urban area in a Neovita sister site in Tanzania[29] found that infants weighing ≤2.00kg were more likely to be hospitalised in the first year of life compared to NLBW infants (aHR=2.74; 95%CI:1.66-4.54); there was little evidence of an association for infants weighing 2.01-2.50kg (aHR=1.05; 95%CI:0.85-1.29). This analysis was restricted to district hospital admissions, so the severity of illnesses among those admitted was likely to be greater than in our analysis, which included admissions to any facility. A study in urban South Africa[30] reported that infants born at <32 weeks' gestation were more likely to be hospitalised for respiratory syncytial virus, bronchiolitis and pneumonia in childhood. The association between preterm delivery and pneumonia was also reported by another South African study, although no association was found for LBW infants[3].

A number of factors may explain why, in a population where birth weight was so strongly associated with death, there was little association with illness or admissions. Our data on illness, care seeking and admissions were based on maternal recall. Recognition of childhood illnesses in low and middle income settings is poor[31], possibly leading to underreporting of illness. We don't know if under-recognition or underreporting in our study was differential by birth weight. Qualitative data from Uganda reported poor recognition of LBW as a danger sign and a consequent lack of care seeking for neonatal illness[32]. A failure to recognise and appreciate the severity of illness among LBW infants who die has also been reported[33].

As health facility admission is a notable event, underreporting is less likely. Admission is a marker for severe disease. However, lack of care-seeking for LBW infants may decrease the opportunity for hospital admission. Although severity is recognised as an important determinant of care seeking[31], it has previously been reported in our study area that care is not sought for up to 50% of severe illnesses[34]. We found an absence of care seeking for LBW infants for all illnesses, including fatal illnesses. Reduced care seeking will have led to reduced opportunities to be admitted, and may have increased the risk of death. This may explain the discordance between our reported admission and mortality rates, especially if absence of care seeking is because care-givers think the infant has a low chance of survival[9]. This would mostly affect the weakest infants at greatest risk of dying. Furthermore, in our study area, some illnesses are considered "not for hospital" and untreatable by modern medicine[34]. We do not know if "not for hospital" illnesses were more prevalent among LBW infants and if this perception overly impacted on care seeking behaviour for LBW infants in our study area.

Short duration of severe illness, suggesting sudden onset or rapid progression, may be more frequent among LBW compared to NLBW infants, resulting in little time to seek care

and higher mortality rates. We lacked data on duration for illnesses reported during routine follow-up. Our analyses of fatal illnesses suggested no differences in illness duration or time to seeking care by birth weight; however, this analysis was limited by low sample size.

Strengths

Due to the population-based nature of the cohort and low numbers excluded from the analyses, our results are likely to be generalisable to the underlying population. The large sample size provided sufficient power for us to generate estimates of mortality for several categories of LBW, including VLBW infants. Our study further benefited from low rates of loss-to-follow-up (<3%) and from highly complete data on mortality, including date of death. This will have minimised bias and potential misclassification of deaths by time-period in our study.

Limitations

We lacked data on gestational age (GA), and so could not generate separate estimates by levels of prematurity or for SGA infants. Data were unavailable for time to illness onset, time to care seeking, type of care sought (other than admissions to a health facility) and for disease severity, factors which may differ among LBW and NLBW infants and which may modify the association between birth weight and illness and mortality. We also lacked health service data on diagnoses of illness and data on cause of death, limiting investigation of the role of LBW in cause-specific morbidity and mortality. Despite the large sample size, the study was under-powered to detect moderate differences in illness or admissions by birth weight, especially in the smaller categories of birth weight stratified by time-period. Recall of dates of illness in our study population was poor, with over 40% of illness start dates reported as unknown. We relied on imputation to assign these illness dates, which may have led to some misclassification by time-period. However, the frequent (monthly) nature of data collection throughout the study allowed almost 75% of all imputed dates to

be imputed within a 30-day window, thus minimising the occurrence of misclassification of dates by time-period.

Conclusions and Recommendations

LBW infants are more likely to die throughout the first year of life and their mothers are less likely to seek care for them when they are sick. Strategies to minimise their mortality should target the entire infant period. Efforts to improve their care seeking are needed. This could include educating mothers of LBW infants about the potential of simple caregiving practices and timely care seeking to improve their infant's chance of survival. Our study highlights the need for robust, prospective, population-based studies in Africa to further investigate the association between birth weight and infant illness, care seeking and care-giving, and how these relate to infant mortality.

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Tables and Figures

Table 1: Characteristics of infants included in the analyses

	Infants included (N=22906) n (%)
Birth weight	
>=2.5kg	19322 (84.4)
2.00-2.49kg	3023 (13.2)
1.50-1.99kg	444 (1.9)
<1.50kg	117 (0.5))
Religion of head of household	
Christian	15961 (69.7)
Muslim	5486 (24.0)
Other	1459 (6.4)
Ethnicity of household	
Akan	10690 (46.7)
Other	12216 (53.3)
Maternal education	
None	7101 (31.0)
Primary school	4232 (18.5)
Post-primary / tertiary	11573 (50.5)
Maternal occupation	
Government/Private/Other	1223 (5.3)
Self-employed	8934 (39.0)
Farming	6642 (29.0)
Does not work	6107 (26.7)
Socioeconomic status	
1 (poorest)	4489 (19.6)
2	4539 (19.8)
3	4576 (20.0)
4	4638 (20.2)
5 (richest)	4664 (20.4)
Exposure to indoor smoke	
Yes	13033 (56.9)
Missing	
Place of delivery	
Facility	17552 (76.6)
Non-facility	5354 (23.4)
Missing	
Distance to nearest health facility	
<1.00km	13856 (60.5)
1.00-4.99km	5282 (23.1)
>=5.00km	3768 (16.4)
Missing	
Maternal age (years)	
15 – 19	2644 (11.5)
20 – 24	5880 (25.7)
25 – 29	6149 (26.8)
30 – 34	4611 (20.1)
35 years and over	3622 (15.8)
Missing	
No. children in family	
0-1	6722 (29.3)
2-3	9137 (39.9)
4 or more	7047 (30.8)
Missing	
Maternal illness	
Yes	1122 (4.9)
Missing	
Infant sex	
Female	11286 (49.3)
Multiple Birth	
Yes	845 (3.7)

Figure 1: Probability of survival in the first year of life, by birth weight

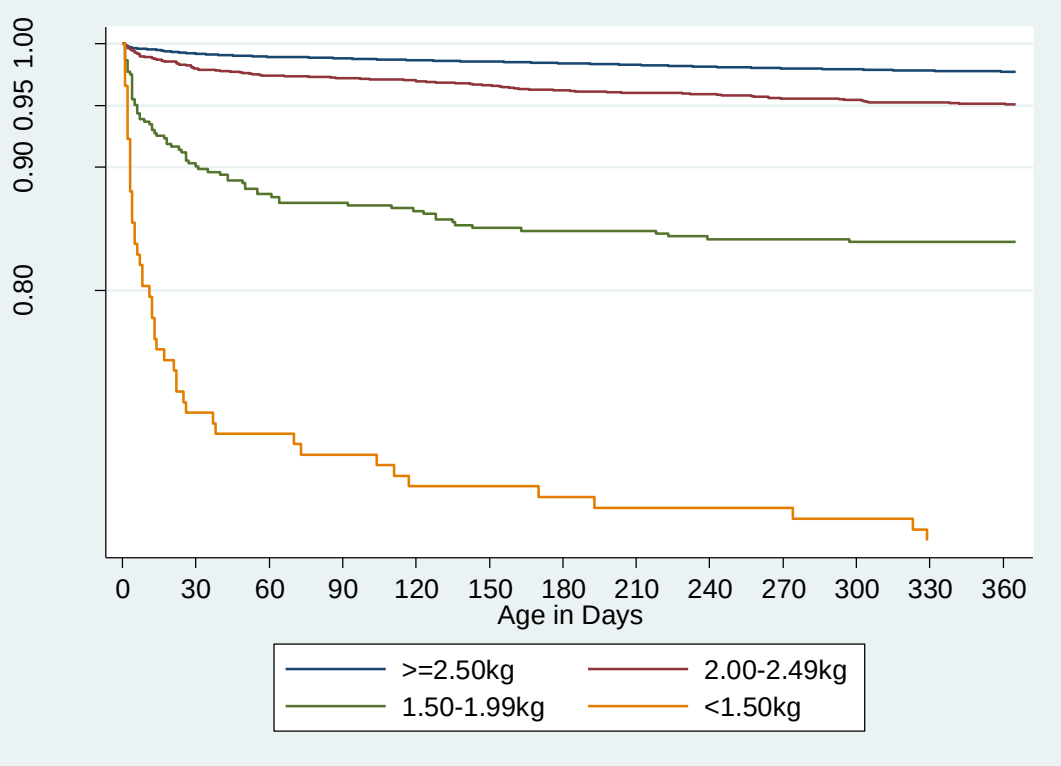

Figure 2: Illness rates by birth weight in the first year of life

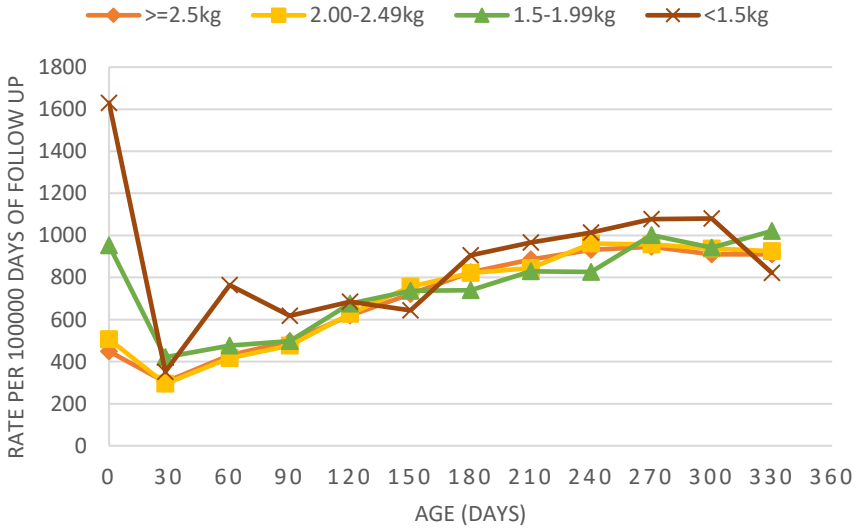

Table 2: The association between birth weight and infant mortality, illness, absence of care seeking and health facility admissions in the first year of life

Birth weight	Outcome / PDOFU[a]	Outcome / 1000 YOFU[b]	Unadjusted HR (95%CI)	Adjusted[C] HR (95%CI)
		Mortality		
>=2.50kg	433/7326996	21.6 (19.6-23.7)	Ref	Ref
2.00-2.49kg	147/1119524	48.0 (40.8-56.4)	2.21 (1.83-2.66)	2.13 (1.76-2.59)
1.50-1.99kg	71/146813	176.6 (140.0-222.9)	7.92 (6.16-10.18)	8.21 (6.26-10.76)
<1.50kg	47/29181	588.3 (442.0-783.0)	24.51 (18.13-33.12)	25.38 (18.36-35.10)
			p<0.0001	*p<0.0001*
Birth weight	**Outcome / PDOFU[a]**	**Outcome / 1000 YOFU[b]**	**Unadjusted RR (95%CI)**	**Adjusted[C] RR (95%CI)**
		Illness		
>=2.50kg	47969/6832406	2564.4 (2541.5-2587.4)	Ref	Ref
2.00-2.49kg	7379/1041876	2586.9 (2528.5-2646.6)	1.01 (0.98-1.04)	0.99 (0.96-1.03)
1.50-1.99kg	1029/136089	2761.7 (2598.1-2935.7)	1.10 (1.01-1.19)	1.06 (0.98-1.14)
<1.50kg	233/26638	3194.9 (2809.9-3632.6)	1.32 (1.12-1.57)	1.15 (0.98-1.36)
			p=0.0012	*p=0.1557*
Birth weight	**Outcome / Total**	**Proportion with outcome (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted[C] OR (95%CI)**
		Absence of care seeking		
>=2.50kg	7680/48115	16.0 (15.6-16.3)	Ref	Ref
2.00-2.49kg	1214/7405	16.4 (15.6-17.3)	1.03 (0.95-1.12)	1.00 (0.91-1.09)
1.50-1.99kg	235/1031	22.8 (20.3-25.5)	1.72 (1.41-2.08)	1.46 (1.18-1.81)
<1.50kg	52/236	22.0 (17.2-27.8)	1.76 (1.18-2.63)	1.05 (0.68-1.63)
			p<0.0001	*p=0.0069*
		Admissions		
>=2.50kg	3496/48115	7.3 (7.0-7.5)	Ref	Ref
2.00-2.49kg	580/7405	7.8 (7.2-8.5)	1.10 (0.98-1.23)	1.12 (1.00-1.26)
1.50-1.99kg	88/1031	8.5 (7.0-10.4)	1.16 (0.88-1.52)	1.12 (0.84-1.48)
<1.50kg	23/236	9.7 (6.6-14.2)	1.46 (0.86-2.48)	1.41 (0.82-2.43)
			p=0.1428	*p=0.1537*

a) PDOFU = person days of follow-up; b) YOFU = years of follow-up; c) adjusted for religion, ethnicity, maternal education, maternal occupation, socioeconomic status, exposure to indoor smoke, place of delivery, distance to the nearest health facility, maternal age, number of living children in family, maternal illness, infant sex, multiple birth.

Table 3: Stratum specific estimates of the association between birth weight and infant mortality, illness, absence of care seeking and health facility admissions in the neonatal, early and late infant periods

	Neonatal			Early Infant			Late Infant		
Birth weight	**Outcome / PDOFU**	**Outcome / 1000 years of follow-up**	**Adjusted[a] HR (95%CI)**	**Outcome / PDOFU**	**Outcome / 1000 years of follow-up**	**Adjusted[a] HR (95%CI)**	**Outcome / PDOFU**	**Outcome / 1000 years of follow-up**	**Adjusted[a] HR (95%CI)**
					Mortality[1]				
>=2.50kg	144/518319	97.9 (83.1-115.2)	Ref	157/2884213	19.1 (16.3-22.4)	Ref	132/3450857	14.1 (11.8-16.7)	Ref
2.00-2.49kg	53/80502	231.9 (177.2-303.6)	2.29 (1.66-3.15)	61/442344	47.1 (36.3-61.0)	2.45 (1.81-3.31)	33/522731	23.2 (16.5-32.6)	1.60 (1.09-2.35)
1.50-1.99kg	45/11146	1357.1 (1006.5-1829.9)	14.71 (10.37-20.86)	22/57927	151.2 (101.4-225.6)	7.22 (4.57-11.42)	4/67449	21.8 (8.2-58.0)	1.61 (0.59-4.39)
<1.50kg	35/2502	4947.3 (3552.1-6890.4)	48.45 (32.81-71.55)	8/11717	249.6 (124.8-499.1)	12.95 (6.30-26.60)	4/12897	113.9 (42.8-303.6)	8.42 (3.09-22.92)
Birth weight	**Outcome / PDOFU**	**Outcome / 1000 years of follow-up**	**Adjusted[a] RR (95%CI)**	**Outcome / PDOFU**	**Outcome / 1000 years of follow-up**	**Adjusted[a] RR (95%CI)**	**Outcome / PDOFU**	**Outcome / 1000 years of follow-up**	**Adjusted[a] RR (95%CI)**
					Illness[2]				
>=2.50kg	2343/537087	1593.4 (1530.2-1659.2)	Ref	14644/2882964	1855.3 (1825.5-1885.6)	Ref	30776/3412047	3294.5 (3257.9-331.5)	Ref
2.00-2.49kg	411/83316	1801.8 (1635.8-1984.7)	1.00 (0.89-1.12)	2246/441850	1856.6 (1781.4-1935.0)	0.99 (0.94-1.04)	4689/516711	3314.5 (3221.0-3410.8)	0.99 (0.96-1.03)
1.50-1.99kg	106/11533	3357.0 (2775.1-4061.0)	1.57 (1.27-1.95)	324/57927	2042.9 (1832.2-2277.9)	1.10 (0.97-1.23)	596/66629	3267.2 (3015.1-3540.3)	0.99 (0.89-1.08)
<1.50kg	42/2534	6053.9 (4473.9-8191.7)	1.58 (1.13-2.21)	67/11543	2120.1 (1668.7-2693.7)	1.10 (0.85-1.43)	122/12561	3547.5 (2970.7-4236.3)	1.07 (0.87-1.32)
Birth weight	**Outcome / Total**	**Proportion with outcome (95%CI)**	**Adjusted[a] OR (95%CI)**	**Outcome / Total**	**Proportion with outcome (95%CI)**	**Adjusted[a] OR (95%CI)**	**Outcome / Total**	**Proportion with outcome (95%CI)**	**Adjusted[a] OR (95%CI)**
					Absence of care seeking[3]				
>=2.50kg	1210/2378	50.9 (48.9-52.9)	Ref	2549/15227	16.7 (16.2-17.3)	Ref	3921/30510	12.9 (12.5-13.2)	Ref
2.00-2.49kg	217/420	51.7 (46.9-56.4)	1.04 (0.81-1.34)	403/2331	17.3 (15.8-18.9)	1.03 (0.90-1.19)	594/4654	12.8 (11.8-13.8)	0.97 (0.86-1.09)
1.50-1.99kg	78/107	72.9 (63.7-80.5)	3.30 (1.98-5.48)	82/333	24.6 (20.3-29.5)	1.74 (1.26-2.39)	75/591	12.7 (10.2-15.6)	0.98 (0.72-1.32)
<1.50kg	30/44	68.2 (53.0-80.3)	2.07 (0.97-4.43)	8/70	11.4 (5.8-21.3)	0.63 (0.27-1.46)	14/122	11.5 (6.9-18.5)	0.85 (0.43-1.66)

Continues….

Continued….

	Admissions[4]								
	Neonatal	**Early Infant**	**Late Infant**		**Neonatal**	**Early Infant**	**Late Infant**		**Neonatal**
Birth weight	**Outcome / Total**	**Proportion with outcome (95%CI)**	**Adjusted[a] OR (95%CI)**	**Outcome / Total**	**Proportion with outcome (95%CI)**	**Adjusted[a] OR (95%CI)**	**Outcome / Total**	**Proportion with outcome (95%CI)**	**Adjusted[a] OR (95%CI)**
>=2.50kg	250/2378	10.5 (9.3-11.8)	Ref	1019/15227	6.7 (6.3-7.1)	Ref	2227/30510	7.3 (7.0-7.6)	Ref
2.00-2.49kg	48/420	11.4 (8.7-14.8)	1.11 (0.77-1.60)	194/2331	8.3 (7.3-9.5)	1.35 (1.12-1.63)	338/4654	7.3 (6.6-8.0)	1.03 (0.89-1.18)
1.50-1.99kg	7/107	6.5 (3.1-13.1)	0.56 (0.24-1.29)	28/333	8.4 (5.9-11.9)	1.19 (0.75-1.89)	53/591	9.0 (6.9-11.6)	1.24 (0.88-1.75)
<1.50kg	6/44	13.6 (6.2-27.4)	1.59 (0.59-4.27)	6/70	8.6 (3.9-17.9)	1.34 (0.51-3.52)	11/122	9.0 (5.1-15.6)	1.36 (0.65-2.85)

a) adjusted for religion, ethnicity, maternal education, maternal occupation, socioeconomic status, exposure to indoor smoke, place of delivery, distance to the nearest health facility, maternal age, number of living children in family, maternal illness, infant sex, multiple birth. *p-values for interaction by time-period = 1) <0.0001, 2) 0.0029, 3) 0.0002, 4) 0.1383*

Table 4: Comparison of illness, care seeking and care-giving behaviour during fatal illnesses among LBW compared to NLBW infants

Indicator	422 NLBW (%)	262 LBW (%)	p-value
Duration of illness			
Duration of fatal illness			
<1d	21 (5.0)	12 (4.6)	
1-7d	216 (51.2)	142 (54.2)	
>7d	185 (43.8)	108 (41.2)	0.7440
Care seeking behaviour			
Sought care			
No	55 (13.0)	60 (22.9)	
Yes	367 (87.0)	202 (77.1)	0.0010
Among 569 infants who sought care:			
Days ill before care sought			
<1d	135 (36.8)	71 (35.2)	
1-3d	174 (47.4)	86 (42.6)	
>3d	58 (15.8)	45 (22.3)	0.1510
Sought professional medical care (from a hospital, clinic, doctor, nurse or pharmacy)			
No	24 (6.5)	29 (14.4)	
Yes	343 (93.5)	173 (85.6)	0.0020
Sought care elsewhere			
No	228 (62.1)	116 (57.4)	
Yes	139 (37.9)	86 (42.6)	0.2730
Care-giving behaviour (among 516 infants who sought professional medical care)			
Admitted to a health facility			
No	179 (52.2)	82 (47.4)	
Yes	164 (47.8)	91 (52.6)	0.3040
Received medical therapy[1]			
No	52 (15.2)	38 (22.0)	
Yes	291 (84.8)	135 (78.0)	0.0540
Died in hospital			
No	162 (47.2)	88 (50.9)	
Yes	181 (52.8)	85 (49.1)	0.4350

1. Infants who were prescribed medicine or received surgery

4.3. FURTHER DISCUSSION ON THE METHODOLOGY USED FOR THE ANALYSES

4.3.1. Considerations in the choice of analytical methodology

The rate of mortality varies rapidly over time in the first year of life. In particular, the rate declines rapidly each day in the first week of life[1]. Given this rapidly changing mortality rate, I considered Cox proportional hazards to be the most appropriate technique to use to assess the relationship between birth weight and mortality. I therefore used it to generate hazard ratios of the association between birth weight and infant mortality, adjusted for all other possible confounders using a causal modelling approach, as described in **Section 3.7.3**. In order to assess the assumption of proportional hazards (that the estimated hazard ratios were proportional over time), I generated a log-log plot (a plot of the log of survival compared to the log of the analysis time). I examined this plot to ensure that there was neither convergence nor divergence of the plots (that the plots were parallel), as confirmation that this assumption was not violated.

Unlike mortality, illness rates do not change rapidly with age. In order to be able to estimate morbidity rates directly from the model, I used random effects Poisson regression to generate rate ratios of the association between birth weight and illness, adjusted for all possible confounders. As infants were followed up monthly for the first year of life, they could experience more than one episode of illness between follow-up visits. I used random effects modelling to control for clustering associated with multiple events per infant.

I did not have data on person-time from the onset of illness to the time of care seeking or hospitalisation. Therefore, I used random-effects logistic regression to assess whether, among infants who fell ill, birth weight was associated with whether care was sought for the infant, or whether the infant was admitted to a health facility.

4.3.2. Why I did not generate estimates by gestational age.

Women who fell pregnant during the Neovita trial were asked to estimate the date of their LMP, both when they were visited every month as part of pregnancy surveillance, and when they delivered. LMP is often used to estimate the GA of infants, and to categorise infants as preterm or term. If I had used these data in this way, I could potentially have generated estimates of mortality and morbidity according to whether the infant was preterm or not. This would have allowed a more direct comparison between my results and

those of other studies, and it would have allowed me to better characterise the risk of illness and death due to preterm delivery and that due to growth retardation.

Overall, the quality of our data on LMP was poor. In our study population, data on LMP was missing for 57.5% of pregnancies (16398/28498) and was inconsistently reported (from one pregnancy surveillance visit to another) for 16.0% (1935/12100) of women reporting to know their LMP. In addition, women in our study area report their pregnancies late, which may have affected the accuracy of our data on LMP.

Furthermore, the use of LMP data to estimate GA can be inaccurate for a number of reasons. Firstly, a number of factors, including uncertain recall of dates, bleeding which is not in fact associated with menses, and delayed ovulation can lead to problems with the reporting of LMP[2]. Data from high-income settings indicate that women with certain LMP dates are systematically different to those with uncertain dates. Those with uncertain dates are more likely to be young, primiparous, and to have lower educational attainment, factors which are also associated with LBW[3]. Consequently, GA based on LMP may be misclassified, and this misclassification may be more common among women who deliver LBW infants. LMP is also subject to digit preference[2].

Secondly, there is poor concordance between GA as assessed by ultrasound (the gold standard for GA assessment) and that estimated using LMP. Therefore, GA estimated from LMP is prone to misclassification. For example, in an analysis of 80 pregnancies in the Gambia[4], LMP classified 18.4% of infants as preterm, compared to 2.5% for ultrasound. Although the mean GA was similar using both methods, there was greater variation for LMP. Another study of 1342 pregnancies in South Africa reported that ultrasound refuted LMP based GA dating in 45% of the studied pregnancies[5].

Given the large volume of missing and inconsistently reported data on LMP in my study population, and given the potential for misclassification of GA based on LMP, particularly for infants at risk of LBW, illness and death I opted not to use these data to estimate GA, as I did not think it would be possible to categorise infants accurately according to whether they were preterm or not.

4.3.3. Why I did not adjust for the effects of breastfeeding.

Breast feeding is known to be associated with the risk of mortality and illness during infancy[6,7]. During the monthly postneonatal follow-up conducted for the Neovita trial, we collected data on infant feeding in the previous 24 hours. It may have been possible to

categorise infants according to whether they were exclusively, partially, or not breastfed, and to examine whether any association between birth weight and illness or death was mediated by breastfeeding. I opted not to do this for a number of reasons. Firstly, this would have entailed categorising an infant's feeding status based on data for one day out of 30. However, during weaning infants may oscillate between exclusive and partial breastfeeding. Furthermore, these data were frequently collected for a time-period that did not coincide with the actual illness (if the illness did not occur in the 24 hours before the follow-up visit). In the event of the data being collected at the time of an illness, infant feeding practices could be influenced by an infant's illness. Sick babies may have altered feeding practices, and so their feeding practices around the time of illness may not reflect their usual feeding practices. Based on the available data, I reasoned that I could not accurately classify infants' feeding status at the time of illness or death.

4.4. CAUSE-SPECIFIC ADMISSIONS

I describe the process for assigning cause specific illness in **Section 3.2**. Briefly, data on cause of illness were only collected for admissions to health facilities and were based on maternal recall only. These data were categorised into three broad categories of infection, non-infection and unknown other, due to the potential for misclassification by cause of illness as described in **Section 3.2**. As reported in the paper, 4187 admissions were reported for 3485 infants who reported illness. Of these admissions 4137 (98.8%) were associated with infections, 586 (14.0%) with non-infections, and 81 (1.9%) with unknown causes. Multiple causes were reported for 459 (11.0%) admissions (including 158 (3.8%) reporting all three causes).

As discussed in **Section 4.1**, if LBW infants are less likely to be vaccinated, they may be more likely to contract VPDs. In the absence of data on VPDs, I was interested in investigating whether LBW infants were more likely to contract infectious diseases. However, I only had data on admissions due to infectious diseases. As the overwhelming majority of admissions (98.8%) had an associated infectious cause, and as overall, no association was found between birth weight and admissions, there was unlikely to be an association between birth weight and infection related admissions. Nonetheless, I investigated this by repeating the analysis of the association between birth weight and admissions, restricting the analysis to infection-related admissions. There was little evidence of an association between birth weight and infection related admissions, in the overall infant period (**Table 4.2**). There was some evidence that the association varied by

time-period (p-value for interaction = 0.0395) (**Table 4.3**). However, evidence of a greater likelihood of infection-related admissions was restricted to infants weighing 2.00-2.49kg in the early infant period only, and the adjusted rate ratios showed no clear pattern.

Although as discussed in the paper, there is some evidence of an association between birth weight and illness in the neonatal period, there is little evidence of an association with overall and infection-related admissions. As these data are based on maternal recall, and as recognition of infant illness is known to be poor[8] these data should be interpreted with caution. Data on whether recognition of illness is worse among LBW infants are lacking; however, it is suspected that this may be the case. The question of whether illness recognition is worse among LBW infants merits further research.

Table 4.2: The association between birth weight and infection-related admissions in the first year of life

Birth weight	Outcome / Total	Proportion with outcome (95%CI)	Unadjusted OR (95%CI)	Adjusted[1] OR (95%CI)
>=2.50kg	3488/48115	7.2 (7.0-7.5)	Ref	Ref
2.00-2.49kg	543/7405	7.3 (6.8-7.9)	1.02 (0.90-1.15)	1.03 (0.91-1.17)
1.50-1.99kg	88/1031	8.5 (7.0-10.4)	1.14 (0.86-1.53)	1.10 (0.81-1.48)
<1.50kg	18/236	7.6 (4.9-11.8)	1.08 (0.59-1.98)	1.06 (0.57-1.96)
			p=0.8151	p=0.8979

1) adjusted for religion, ethnicity, maternal education, maternal occupation, socioeconomic status, exposure to indoor smoke, place of delivery, distance to the nearest health facility, maternal age, number of living children in family, maternal illness, infant sex, multiple birth

Table 4.3: The association between birth weight and infection related admissions in the neonatal, early, and late infant periods[1].

	Neonatal			Early Infant			Late Infant		
Birth weight	Outcome / Total Illness Episode	Proportion with outcome (95%CI)	Adjusted[2] OR (95%CI)	Outcome / Total Illness Episode	Proportion with outcome (95%CI)	Adjusted OR (95%CI)	Outcome / Total Illness Episode	Proportion with outcome (95%CI)	Adjusted OR (95%CI)
>=2.50kg	202/2378	8.5 (7.4-9.7)	Ref	1016/15227	6.7 (6.3-7.1)	Ref	2270/30510	7.4 (7.2-7.7)	Ref
2.00-2.49kg	38/420	9.0 (6.6-12.2)	1.05 (0.70-1.59)	188/2331	8.1 (7.0-9.2)	1.30 (1.07-1.58)	317/4654	6.8 (6.1-7.6)	0.92 (0.79-1.07)
1.50-1.99kg	5/107	4.7 (1.9-10.8)	0.47 (0.17-1.27)	27/333	8.1 (5.6-11.6)	1.11 (0.68-1.80)	56/591	9.5 (7.4-12.1)	1.25 (0.87-1.78)
<1.50kg	3/44	6.8 (2.2-19.3)	0.86 (0.23-3.19)	5/70	7.1 (3.0-16.1)	1.00 (0.34-2.92)	10/122	8.2 (4.5-14.6)	1.19 (0.53-2.64)

1) p-value for interaction by time-period = 0.0395

2) adjusted for religion, ethnicity, maternal education, maternal occupation, socioeconomic status, exposure to indoor smoke, place of delivery, distance to the nearest health facility, maternal age, number of living children in family, maternal illness, infant sex, multiple birth

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CHAPTER 5: DELAYED VACCINATION OF LOW BIRTH WEIGHT INFANTS

Preamble

The paper presented in this chapter addresses PhD objective 2, namely to investigate birth weight and other factors as determinants of postneonatal vaccination, using DTP1 and DTP3 as indicator vaccines. In ***Section 5.1****. I provide a brief overview of the paper. In* ***Section 5.2.*** *I present the paper itself, which was published in the Bulletin of the World Health Organisation in June 2016. In* ***Sections 5.3.*** *and* ***5.4.*** *I outline factors considered in the design of the study and in the choice of methods used for the statistical analysis. In* ***Section 5.5.*** *I discuss the extent to which the design of the study may have biased the estimates of the association between birth weight and vaccination. In* ***Section 5.6.*** *I present the results of two sensitivity analyses to assess the impact of my decision to include infants in my analyses who were missing vaccination cards, but whose mothers consistently reported them as not vaccinated, (as originally discussed in* ***Chapter 3****). In* ***Section 5.7.*** *I present additional results that were excluded from the main paper, and I include a discussion of these results.*

5.1. INTRODUCTION

This paper presents the results of a prospective population-based cohort study to investigate birth weight and other factors as determinants of DTP1 and DTP3 vaccination in the postneonatal period. The study population for each of the DTP1 and DTP3 analyses comprised 22361 and 22192 infants respectively with known vaccination status, and full covariate data who were in follow-up at the respective vaccine due dates. The outcomes for each of the analyses were vaccination rate ratios at 10, 14 and 18 weeks after birth for DTP1, and at 18, 22 and 24 weeks after birth for DTP3 (4, 8 and 12 weeks after each of the vaccine due dates), calculated using Poisson regression. I adjusted all estimates a priori for potential confounders.

5.2. PAPER 2: VACCINATION TIMING OF LOW-BIRTH-WEIGHT INFANTS IN RURAL GHANA: A POPULATION-BASED, PROSPECTIVE COHORT STUDY

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Maureen O'Leary
Principal Supervisor	Sara Thomas
Thesis Title	Low birth weight as a risk factor for under-vaccination in rural Ghana; evidence from a population based cohort

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	Bulletin of the World Health Organisation		
When was the work published?	June 2016		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	No	Was the work subject to academic peer review?	Yes

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Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Karen Edmond came up with the original concept for this research, and I further developed this concept in collaboration with her. This research is based on a secondary analysis of data collected as part of a randomised control trial of neonatal vitamin A supplementation. I was the epidemiologist on the trial and I spent 3 years in Ghana overseeing and ensuring the quality of the data collected for the trial and subsequently included in this research. I cleaned the data with some assistance from Lu Gram. I prepared the datasets used in the analyses. I designed the research and developed a detailed plan of analysis, with supervision and input from Sara Thomas and Sian Floyd. In particular Sara Thomas advised on the choice of analytical methodology used for the analysis. I discussed in detail with Sara Thomas and Sian Floyd the selection of risk periods for the analyses, and issues of bias introduced by the study design. I wrote the program for the analyses, ran the analyses and drafted the manuscript. Sara Thomas, Sian Floyd and Karen Edmond provided advice on the interpretation of the results. Sara Thomas gave valuable input on early drafts of the manuscript. All co-authors commented on the manuscript. The article was peer-reviewed, and I edited the manuscript in accordance with the reviewers' comments, with advice from the co-authors.

Student Signature:  **Date:** 27/7/16

Supervisor Signature:  **Date:** 27/7/16

Vaccination timing of low-birth-weight infants in rural Ghana: a population-based, prospective cohort study

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Objective To investigate delays in first and third dose diphtheria–tetanus–pertussis (DTP1 and DTP3) vaccination in low-birth-weight infants in Ghana, and the associated determinants.

Methods We used data from a large, population-based vitamin A trial in 2010–2013, with 22 955 enrolled infants. We measured vaccination rate and maternal and infant characteristics and compared three categories of low-birth-weight infants (2.0–2.4 kg; 1.5–1.9 kg; and < 1.5 kg) with infants weighing ≥ 2.5 kg. Poisson regression was used to calculate vaccination rate ratios for DTP1 at 10, 14 and 18 weeks after birth, and for DTP3 at 18, 22 and 24 weeks (equivalent to 1, 2 and 3 months after the respective vaccination due dates of 6 and 14 weeks).

Findings Compared with non-low-birth-weight infants ($n = 18\,979$), those with low birth weight ($n = 3382$) had an almost 40% lower DTP1 vaccination rate at age 10 weeks (adjusted rate ratio, aRR: 0.58; 95% confidence interval, CI: 0.43–0.77) and at age 18 weeks (aRR: 0.63; 95% CI: 0.50–0.80). Infants weighing 1.5–1.9 kg ($n = 386$) had vaccination rates approximately 25% lower than infants weighing ≥ 2.5 kg at these time points. Similar results were observed for DTP3. Lower maternal age, educational attainment and longer distance to the nearest health facility were associated with lower DTP1 and DTP3 vaccination rates.

Conclusion Low-birth-weight infants are a high-risk group for delayed vaccination in Ghana. Efforts to improve the vaccination of these infants are warranted, alongside further research to understand the reasons for the delays.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

Approximately 14% of infants born in low- and middle-income countries have a low birth weight (weighing < 2.50 kg at birth).[1] It has been reported that in high-income settings, low-birth-weight infants have an increased risk of vaccine-preventable diseases, such as pertussis,[2] invasive pneumococcal disease[3–5] and *Haemophilus influenzae* type b (Hib).[6] However, it is not known whether such risk exists in low-income settings. Timely vaccination of low-birth-weight infants, including booster doses, is important because these infants have lower passive immunity before vaccination[7] and may respond sub-optimally to primary vaccination.[8] Vaccination has similar efficacy and safety in low-birth-weight infants compared with non-low-birth-weight infants,[8] and therefore vaccination is recommended at the same chronological age as other infants.[9]

Studies from high-income settings indicate that low-birth-weight infants are vaccinated later than non-low-birth-weight infants.[10,11] Regardless of whether they are at increased risk, delayed vaccination of low-birth-weight infants prolongs their risk period for contracting vaccine-preventable diseases, especially Hib and *Streptococcus pneumoniae*,[3,12] which are most prevalent in the first few months of life. Studies of the effect of low birth weight on timely vaccination in low-income settings, however, are lacking.

We aimed to measure the timing of vaccination of low-birth-weight infants compared with non-low-birth-weight infants by analysing data from a population-based, prospective cohort study in Ghana. Our primary objectives were to assess whether low birth weight is a determinant of delayed first and third dose diphtheria–tetanus–pertussis (DTP1 and DTP3) vaccination; and whether maternal education or socioeconomic status modified the association between birth weight and vaccination with DTP1 and DTP3. As a secondary objective, we aimed to quantify other determinants of delayed DTP1 and DTP3 vaccination.

Methods

Study design and setting

We studied a cohort of infants nested within a large randomized, double-blind, placebo-controlled trial of neonatal vitamin A supplementation conducted in Ghana between August 2010 and February 2013.[13] The trial was conducted at the Kintampo Health Research Centre in Kintampo, Ghana. The trial procedures and study area have been described elsewhere.[14]

Ethics approval for the study was granted by the ethics committees of the World Health Organization (WHO), the

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London School of Hygiene & Tropical Medicine and the Kintampo Health Research Centre.

DTP vaccination in Ghana is recommended at 6, 10 and 14 weeks of age. Children are vaccinated at health facilities, community health planning system compounds or mobile outreach clinics. For each administered vaccine, the date and place of administration and vaccine batch number are usually documented in the child health record book. These may also be documented on a vaccination card or in the mother's antenatal card. Infants who have never attended a child health clinic may not have a written record.

Enrolment and data collection

Trained fieldworkers enrolled all consenting women aged 15–49 years residing in the study area into a reproductive surveillance system to document pregnancies and deliveries. All infants born in the study area were assessed for eligibility (eligible infants were aged ≤ 3 days at screening, could suck or feed and were staying in the study area for 6 months after enrolment) and mothers were asked for informed written consent for enrolment in the trial. Infants were weighed using calibrated electronic (38%; 8723 of enrolled infants) or spring (62%; 14 232) scales, to record birth weights to the nearest 0.1 kg (electronic scales) or 0.2 kg (spring scales). Only five (0.2%) infants were weighed later than 72 hours after delivery. The fieldworkers collected data on infant (sex and multiple delivery), maternal (age, education, occupation, and illness before delivery) and household characteristics (ethnicity, religion, socioeconomic status, distance to health facility and number of children in household).

The enrolled infants were visited monthly for the first year of life to collect data on the types and dates of vaccines given. We looked for written documentation of vaccines from all possible sources, including the child health record book, the mother's antenatal card and vaccination cards. The infant's caregiver (usually the mother) was also asked to recall what vaccines had been given. We also collected data on the infant's vital status and on illnesses since the previous visit.

Follow-up started at birth. It ended at the vaccination date for vaccinated infants, and the end of the risk period for unvaccinated infants not lost to follow-up. For those lost to follow-up before the end of the risk period, follow-up ended on the last date the written record was viewed, for unvaccinated infants whose record was viewed; or on the last date the infant was seen, for unvaccinated infants whose record was never viewed; or on the date of death, for unvaccinated infants who died before the end of the risk period and whose record was viewed after their death.

For the analyses we included all infants from the trial with known vaccination status and dates and with complete data on covariates. We excluded infants who were lost to follow-up or died before the vaccination due date.

Definitions

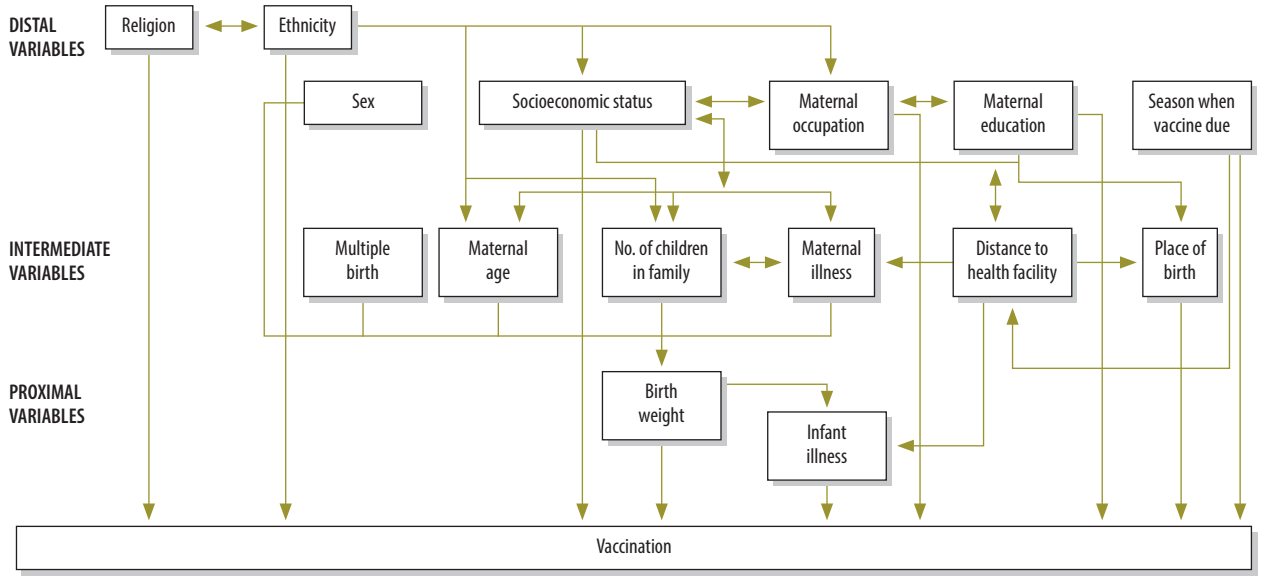
We classified infants' vaccination status as follows: (i) vaccinated, date known (written record had a plausible vaccination date); (ii) vaccinated, date unknown (record had clearly documented vaccination but with the date missing, illegible or implausible); (iii) unvaccinated (record was seen but had no documented vaccination date or any evidence of vaccination; or record was never seen and mother consistently reported infant had never been vaccinated); or (iv) vaccination status unknown (mother reported that infant had been vaccinated but did not specify the vaccine; or infant was never seen in follow-up).

We categorized birth weight into four standard categories: ≥ 2.5 kg (i.e. non-low birth weight); 2.0–2.4 kg; 1.5–1.9 kg; < 1.5 kg.[1,15]

Outcome measures

The study outcomes were delayed receipt of DTP1 and DTP3. There is no standard

Fig. 1. **Hierarchical framework of determinants of infant vaccination in the prospective cohort study in rural Ghana, 2010–2013**



Note: The effects of distal variables were hypothesized to be mediated by intermediate and proximal variables, and intermediate variables by the proximal variables. Among the proximal variables, illness was hypothesized to mediate the effect of birth weight. Mediation is indicated by arrows linking the variables across different levels.

approach to the assessment of delayed vaccination and several definitions based on predefined cut-offs have been described.[16–18] To assess how the effect of birth weight may vary over time, we defined risk periods for delayed vaccination up to 4, 8 and 12 weeks after the vaccination due date. For DTP1 we therefore analysed vaccination rates from birth up to 10, 14 and 18 weeks of age. For DTP3 we analysed vaccination from birth up to 18, 22 and 26 weeks of age.

Data analysis

The data were double-entered and processed at the Kintampo Health Research Centre using the SQL Server 2008 data management system (Microsoft Corp., Redmond, USA). Inconsistencies and errors in the vaccination dates were corrected, with senior fieldworkers visiting mothers to review the written record and verify the dates if necessary.

All analyses were conducted using the Stata package version 13.1 (StataCorp, College Station, USA). We generated Kaplan–Meier curves of time to vaccination in low-birth-weight compared with non-low-birth-weight infants in the first year of life for DTP1 and DTP3. Vaccination rate ratios, adjusted for a priori selected factors, were obtained for each risk period using multivariable Poisson regression, informed by a hierarchical framework of the recognized determinants of vaccination (Fig. 1).[12,16–18] The initial model included distal determinants of vaccination, then intermediate determinants were added, followed by birth weight and, finally, infant illness at the time the vaccine was due (as this was considered to be a possible mediator of the association between birth weight and vaccination).[19] We assessed the statistical association between vaccination and each explanatory variable using likelihood ratio tests and 95% confidence intervals (CI). We also investigated whether the association between birth weight and vaccination varied by maternal education or socioeconomic status by testing the interaction of birth weight with these variables.

Two sets of sensitivity analyses were undertaken. First, to assess whether delayed DTP3 vaccination simply reflected delayed DTP1 vaccination, we repeated the DTP3 analyses, starting follow-up at receipt of DTP1 vaccination and ending 12 weeks after receipt of DTP1. Second, to examine the effect of possible misclassification of vaccine status for infants categorized as never vaccinated but whose written record was never viewed, we excluded these infants and repeated the analyses of DTP1 vaccination up to 18 weeks from birth and DTP3 vaccination up to 26 weeks.

Results

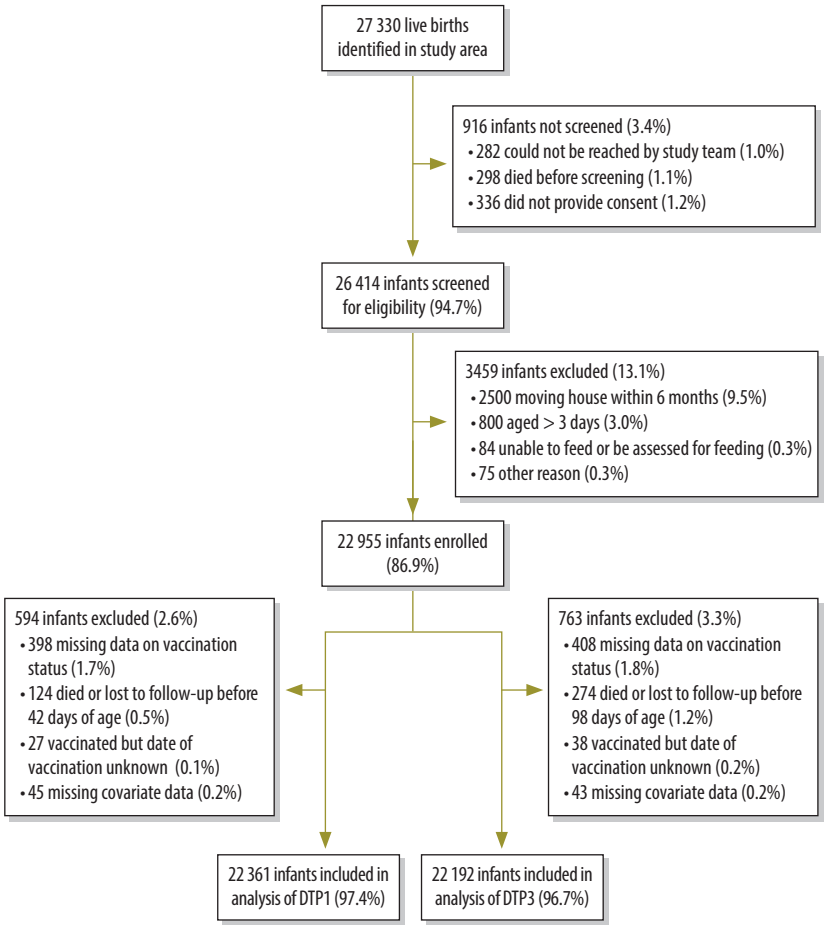
Of 27 330 live births identified in the study area, 26 414 infants were screened for eligibility for the trial and 22 955 were enrolled (Fig. 2); 22 361 (97.4%) and 22 192 (96.7%) infants were included in the analysis of DTP1 and DTP3 respectively. Low-birth-weight infants were more likely to be excluded from our analysis, as were those with illness reported around the vaccination due date, those from multiple births and those born to mothers of lower socioeconomic status, of non-Akan ethnicity, with lower education, with lower employment grades or living more than 5.0 km from a health facility (Table 1). Of the infants included in the DTP1 analysis, 18 979 (84.9%) were normal birth weight and 3382 (15.1%) were low birth weight: 2916 (13.0%) weighed 2.0–2.4 kg, 386 (1.7%) 1.5–1.9 kg and 80 (0.4%) < 1.5 kg. The birth weight distribution was the same for infants in the DTP3 analysis: 18 850 (84.9%) weighed ≥ 2.5 kg, 2886 (13.0%) 2.0–2.4 kg, 378 (1.7%) 1.5–1.9 kg and 78 (0.4%) < 1.5 kg (Table 1).

Delayed vaccination

Birth weight

Although uptake of vaccination was high (> 95%) for all infants by 1 year of age, low birth weight was associated with later vaccination for both DTP1 and DTP3. Median ages at DTP1 vaccination were 8 weeks (interquartile range, IQR: 6.7–9.6 weeks) for infants

Fig. 2. **Identification, recruitment and inclusion of participants in the prospective cohort study on infant vaccination in rural Ghana, 2010–2013**



DTP1: first dose of diphtheria–tetanus–pertussis vaccine; DTP3: third dose of diphtheria–tetanus–pertussis vaccine.
Note: Overall and disaggregated percentages may not agree due to rounding.

Table 1. **Characteristics of infants vaccinated with first and third doses of diphtheria–tetanus–pertussis vaccine in the prospective cohort study in rural Ghana, 2010–2013**

Characteristic	No. (%)			
	DTP1		DTP3	
	Included infants (*n* = 22 361)	Excluded infants (*n* = 594)	Included infants (*n* = 22 192)	Excluded infants (*n* = 763)
Distal determinants				
Religion of head of household				
Christian	15 616 (69.8)	363 (61.1)	15 497 (69.8)	482 (63.2)
Muslim	5 333 (23.8)	178 (30.0)	5 294 (23.9)	217 (28.4)
None/traditional/other	1 412 (6.3)	53 (8.9)	1401 (6.3)	64 (8.4)
Ethnicity of household				
Akan	10 470 (46.8)	223 (37.5)	10 410 (46.9)	283 (37.1)
Other	11 891 (53.2)	371 (62.5)	11 782 (53.1)	480 (62.9)
Socioeconomic status[a]				
1 (poorest)	4 356 (19.5)	155 (26.1)	4 299 (19.4)	212 (27.8)
2	4 407 (19.7)	143 (24.1)	4 363 (19.7)	187 (24.5)
3	4 469 (20.0)	113 (19.0)	4 440 (20.0)	142 (18.6)
4	4 544 (20.3)	100 (16.8)	4 523 (20.4)	121 (15.9)
5 (richest)	4 585 (20.5)	83 (14.0)	4 567 (20.6)	101 (13.2)
Maternal occupation				
Government/private/other	1 200 (5.4)	25 (4.2)	1 199 (5.4)	26 (3.4)
Self-employed	8 752 (39.1)	194 (32.7)	8 716 (39.3)	230 (30.1)
Farming	6 472 (28.9)	199 (33.5)	6 411 (28.9)	260 (34.1)
Not working	5 937 (26.6)	176 (29.6)	5 866 (26.4)	247 (32.4)
Maternal education				
None	6 913 (30.9)	214 (36.0)	6 845 (30.8)	282 (37.0)
Primary school	4 115 (18.4)	121 (20.4)	4 081 (18.4)	155 (20.3)
Secondary/tertiary	11 333 (50.7)	245 (41.2)	11 266 (50.8)	312 (40.9)
Missing values	0 (0.0)	14 (2.4)	0 (0.0)	14 (1.8)
Season when vaccine due: wet	14 176 (63.4)	382 (64.3)	10 406 (46.9)	347 (45.5)
Infant sex: female	11 025 (49.3)	281 (47.3)	10 938 (49.3)	368 (48.2)
Intermediate determinants				
Maternal age (years)				
< 20	2 550 (11.4)	95 (16.0)	2 514 (11.3)	131 (17.2)
20–24	5 714 (25.6)	173 (29.1)	5 657 (25.5)	230 (30.1)
25–29	6 017 (26.9)	137 (23.1)	5 986 (27.0)	168 (22.0)
30–34	4 522 (20.2)	95 (16.0)	4 497 (20.3)	120 (15.7)
≥ 35	3 558 (15.9)	64 (10.8)	3 538 (15.9)	84 (11.0)
Missing value	0 (0.0)	30 (5.1)	0 (0.0)	30 (3.9)
No. of children in family				
0–1	6 516 (29.1)	216 (36.4)	6 450 (29.1)	282 (37.0)
2–3	8 946 (40.0)	209 (35.2)	8 887 (40.0)	268 (35.1)
≥ 4	6 899 (30.9)	169 (28.5)	6 855 (30.9)	213 (27.9)
Maternal illness: yes	1 093 (4.9)	30 (5.1)	1 090 (4.9)	33 (4.3)
Distance from health facility (km)				
< 1.0	13 545 (60.6)	342 (57.6)	13 461 (60.7)	436 (57.1)
1.0–4.9	5 147 (23)	117 (19.7)	5 106 (23.0)	151 (19.8)
≥ 5.0	3 669 (16.4)	133 (22.4)	3 625 (16.3)	169 (22.1)
Missing value	0 (0.0)	2 (0.3)	0 (0.0)	7 (0.9)
Place of birth: health facility	17 155 (76.7)	426 (71.7)	17 047 (76.8)	534 (70.0)
Multiple birth	795 (3.6)	52 (8.8)	784 (3.5)	63 (8.3)

(*continues. . .*)

(. . .*continued*)

Characteristic	No. (%)			
	DTP1		DTP3	
	Included infants (*n* = 22 361)	Excluded infants (*n* = 594)	Included infants (*n* = 22 192)	Excluded infants (*n* = 763)
Distal determinants				
Birth weight (kg)				
≥ 2.5	18 979 (84.9)	382 (64.3)	18 850 (84.9)	511 (67.0)
2.0–2.4	2 916 (13.0)	115 (19.4)	2 886 (13.0)	145 (19.0)
1.5–1.9	386 (1.7)	58 (9.8)	378 (1.7)	66 (8.7)
< 1.5	80 (0.4)	37 (6.2)	78 (0.4)	39 (5.1)
Missing value	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.3)
Mediating variables				
Infant illness: yes	2 748 (12.3)	155 (26.1)	3 429 (15.5)	277 (36.3)
Missing value	0 (0.0)	261 (43.9)	0 (0.0)	329 (43.1)

DTP1: first dose of diphtheria–tetanus–pertussis vaccine; DTP3: third dose of diphtheria–tetanus–pertussis vaccine.
[a] Socioeconomic status was calculated by principal components analysis from an inventory of household assets.

weighing ≥ 2.5 kg at birth; 8.3 weeks (IQR: 6.9–9.9) for those 2.0–2.4 kg; 8.4 weeks (IQR: 6.9–10.7) for those 1.5–1.9 kg and 9 weeks (IQR: 7.4–11.9) for those < 1.5 kg. For DTP3, the corresponding median ages at vaccination were 18.4 weeks (IQR: 16.3–22.1), 18.6 weeks (IQR: 16.6–22.3), 19.6 weeks (IQR: 16.6–23.3) and 20.4 weeks (IQR: 17.7–25.1), respectively.

The Kaplan–Meier curves showed that DTP1 vaccination rates over the days since birth were also lower for infants weighing < 1.5 kg and those weighing 1.5–1.9 kg compared with those weighing ≥ 2.5 kg (Fig. 3). After adjustment for other variables, there was evidence of progressively delayed vaccination with decreasing birth weight (*P*-value for trend < 0.0001). Infants weighing < 1.5 kg at birth had a DTP1 vaccination rate approximately 40% lower than non-low-birth-weight infants by the age of 10 weeks (adjusted rate ratio, aRR: 0.58; 95% CI: 0.43–0.77) and age 18 weeks (aRR: 0.63; 95% CI: 0.50–0.80). Infants weighing 1.5–1.9 kg had vaccination rates approximately 25% lower than non-low-birth-weight infants at these time points (aRR: 0.71; 95% CI: 0.62–0.81 and aRR: 0.76; 95% CI: 0.69–0.85, respectively; Table 2, available at: http://www.who.int/bulletin/volumes/94/5/15-159699).

Similar results were observed for DTP3 (Fig. 3). The findings were also similar for DTP1 and DTP3 vaccination at 8 weeks after the due date (Table 2).

Adjusting for illness had little effect on the magnitude of the association between birth weight and vaccination for both DTP1 and DTP3 (Table 2).

Other variables

Younger maternal age, lower educational attainment, and longer distance to the nearest health facility were associated with moderate reductions in the DTP1 and DTP3 vaccination rates of approximately 10–20% at ages 10 and 18 weeks, whereas higher employment grade was associated with moderate increased vaccination rates at these ages (Table 3, available at: http://www.who.int/bulletin/volumes/94/5/15-159699). In the final model (after adjusting for potential mediating variables) low socioeconomic status of mothers was associated with a 15% increased DTP3 vaccination rate at 18 weeks, whereas no association with DTP1 vaccination was observed. Muslim religion and larger family size were associated with > 10% reduction in DTP3 vaccination rates but had no, or only a small, association with DTP1 vaccination rates. None of the other variables measured had notable associations with DTP1 or DTP3 vaccination rates at any ages.

Sensitivity analyses

Adjusting for late vaccination with DTP1 decreased the effect size for the association between birth weight and the rate of DTP3 vaccination for infants weighing 1.5–1.9 kg (12 weeks after DTP1 aRR: 0.98; 95% CI: 0.85–1.13) compared with an aRR of 0.82 (95% CI: 0.73–0.92) at 12 weeks after the DTP3 due date, but the effect size for infants weighing < 1.5 kg was largely unchanged (Table 2).

Excluding unvaccinated infants whose written record was never seen had little impact on the effect size of the explanatory variables for DTP1 or DTP3.

Modifying factors

When we looked at other factors that might modify the association between birth weight and delayed vaccination there was no evidence that the effect of birth weight on vaccination with DTP1 or DTP3 varied by socioeconomic status (*P*-values for interaction all > 0.4), or that the rate of vaccination with DTP1 varied by maternal education, when measured at age 10 weeks ($P = 0.3338$) or age 18 weeks ($P = 0.2675$). However, for DTP3 vaccination there was some evidence that the effect of birth weight on the vaccination rate at age 18 weeks ($P = 0.0219$) and age 26 weeks ($P = 0.0813$) varied with maternal education, with a more pronounced reduction in vaccination rate among smaller infants born to mothers with higher educational attainment (aRR for infants weighing < 1.50 kg at age 18 weeks: 0.37; 95% CI: 0.19–0.72; aRR at 26 weeks: 0.63; 95% CI: 0.50–0.80). When infants with delayed receipt of DTP1 were excluded from the analysis, this effect was no longer apparent.

Discussion

The results of this study provide evidence that low-birth-weight infants in Ghana are vaccinated later than non-low-birth-weight infants. The ef-

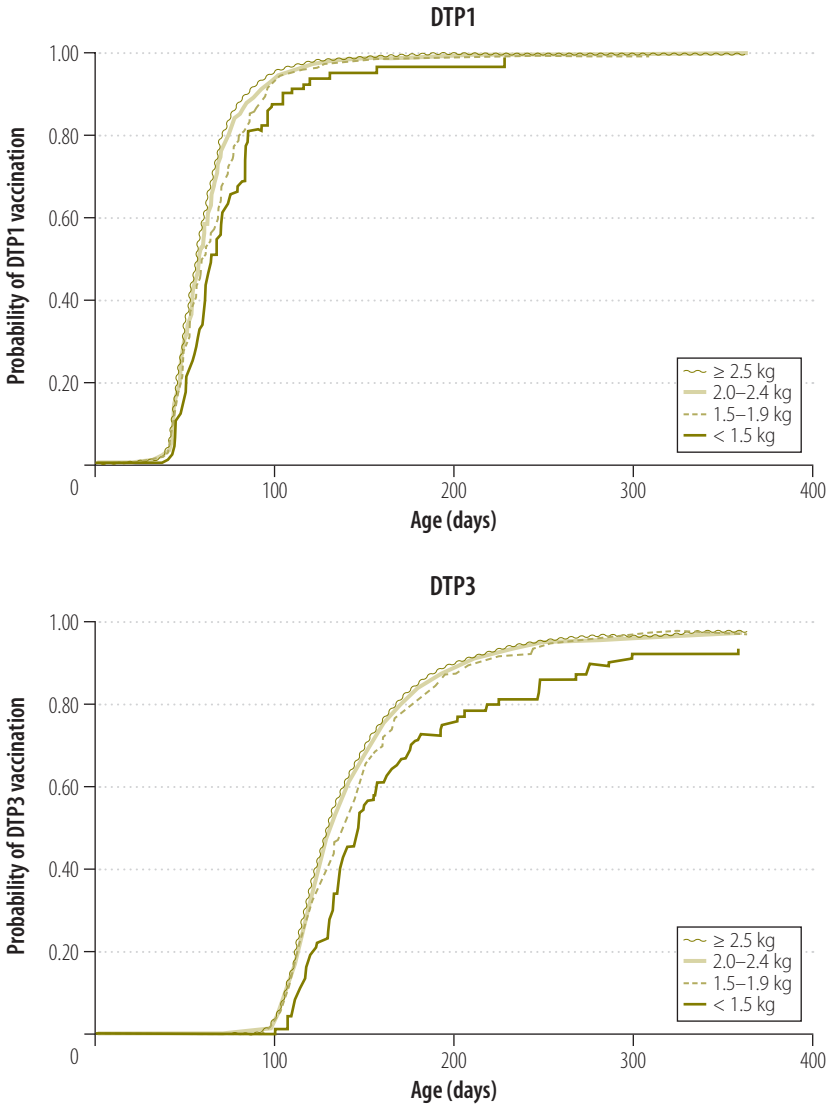
fect persisted up to 12 weeks after the vaccination due date and was evident for both DTP1 and DTP3, even after controlling for other determinants of delayed vaccination.

The results are consistent with previous reports from high-income countries of delayed vaccination in low-birth-weight infants.[10,11,20–22] In addition, a study of low-birth-weight infants in Guinea-Bissau, which did not look at timeliness, reported lower uptake of DTP1 at 8 weeks of age among smaller low-birth-weight infants compared with larger low-birth-weight infants.[23] A North American study reported that both parents and vaccine-providers had erroneous beliefs that initiation of vaccination depended on the degree of prematurity and the infant's weight.[22] In addition, a review of 47 studies in the grey literature from low-income settings reported parental reluctance to bring sick, weak or malnourished children for vaccination for reasons of social stigma and fatalism; these have also been cited as reasons for non-vaccination by vaccine providers.[19]

Low-birth-weight infants in low-income settings are known to have higher rates of illness and death in the first year of life than non-low-birth-weight infants.[15,24–27] Data from high-income settings indicate that they also have higher rates of illness from vaccine-preventable diseases.[2–4,6] The risk and consequences of illness related to vaccine-preventable diseases in low-birth-weight infants in low-income settings is not known and may differ from those in high-income settings. Without this information it is difficult to fully understand the implications of delayed vaccination on clinical outcomes for these infants. However, we do know that delayed vaccination of these infants will prolong their risk period for contracting these diseases and may also reflect an underuse of health services by the caregivers of these infants. Given this increased risk of illness and death, it is essential that all opportunities for vaccination and health care for low-birth-weight infants be exploited.

We also identified several additional determinants of delayed vaccination – low maternal age and educational attainment and longer distance to the nearest health facility – that reflect persisting inequities in access to and uptake of vaccination in our study population. This is consistent with previous findings from the study area[16] and the issue of inequities in coverage of vaccination have featured in global vaccine policy.[28]

Fig. 3. **Time to vaccination with first dose and third dose of diphtheria–tetanus–pertussis vaccine, by birth weight in the prospective cohort study in rural Ghana, 2010–2013**



DTP1: first dose of diphtheria–tetanus–pertussis vaccine; DTP3: third dose of diphtheria–tetanus–pertussis vaccine.

The strengths of our study include the high quality population-based surveillance system and low loss to follow-up. Almost all infants were weighed within 72 hours of delivery by trained fieldworkers using calibrated scales, thus minimizing the likelihood of misclassification of infants by birth weight. Similarly, we collected high quality data on vaccination – from both written records and maternal recall – and we employed a rigorous approach to resolving inconsistencies in these data. Although recall data is used in the generation of routine vaccine uptake estimates,[29] their validity may vary.[30,31] The validity of our recall data was maximized by the continuous nature of the data collection in our study. Infants with recall data accounted for less than 0.6% of all infants included in the analyses and had little impact on our estimates. Furthermore, the inclusion of over 22 000 infants ensured that the study had sufficient power to show effects in small subgroups.

Aspects of this study that may have affected the generalizability of our findings are that our study sample may have experienced more timely vaccination

compared with the general population. A higher proportion of low-birth-weight infants than non-low-birth-weight infants were excluded from our analyses, either because they did not meet the inclusion criteria for enrolment in the trial or because more of them were lost to follow-up or had missing data (including missing vaccination data) than non-low-birth-weight infants. Those excluded could have experienced greater delay in receiving their vaccines compared with the included low-birth-weight infants, possibly causing some underestimation of the association between low birth weight and timely vaccination in our population. As less than 5% of enrolled infants were excluded, this was unlikely to have changed the results appreciably and important delays in vaccination were still observed among low-birth-weight infants. Mothers of enrolled infants were asked about their infant's vaccination status at monthly visits, possibly increasing their awareness of the need to vaccinate their infants. This increased awareness, however, would not have been differentially affected by birth weight and would lead to an overall underestimation of delayed vaccination.

Other limitations are that we did not have reliable data on gestational age and therefore we were not able to assess whether delayed vaccination was associated with prematurity or whether all low-birth-weight infants were affected regardless of gestational age. This study was also not designed to assess the association between delayed vaccination and clinical outcomes such as vaccine-preventable diseases or hospitalizations. Consequently, we do not know whether those infants who had delayed vaccination were more likely to contract vaccine-preventable diseases or to report elevated rates of illness or hospitalization. Eleven explanatory variables were included in our secondary analysis, thus increasing the potential for type 1 errors (finding statistically significant results by chance alone). Finally, we did not collect any qualitative data on the reasons for delayed vaccination of low-birth-weight infants in our study sample. This limits our interpretation of the findings. It may be that vaccination was delayed for reasons beyond the control of both the caregivers and the vaccine providers, such as lack of vaccines or staff, although it is reasonable to assume that these would not be distributed differently among low-birth-weight compared with non-low-birth-weight infants.

Recommendations

Current global policy on vaccination advocates the identification of groups that are underserved by vaccination,[28] yet data on uptake and timeliness of vaccination in low-birth-weight infants are not currently included in routine evaluations of vaccination programmes. These data are feasible to collect in low-income settings; doing this would contribute to a more comprehensive evaluation of the performance of vaccination programmes and would inform the development of strategies to improve uptake and timing of vaccination in all countries.[28] Even though several organizations in high-income countries have made specific recommendations about vaccination of low-birth-weight infants,[9,32] international guidelines are lacking.

Efforts to improve the vaccination of low-birth-weight infants, for example by education of caregivers and vaccine-providers, are warranted. Further research is needed in low-income countries to understand the reasons for delayed vaccination of low-birth-weight infants and to inform strategies to improve the timeliness of vaccination. ■

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ملخص

تحديد مواعيد تلقي الأطفال الرضع منخفضي الوزن عند الولادة للقاحات اللازمة في المناطق الريفية في غانا: دراسة أترابية استباقية قائمة على قطاعات سكانية

الغرض استقصاء التأخر في تلقي الجرعة الأولى والثالثة من اللقاح ضد الدفتريا والتيتانوس والسعال الديكي (جرعة اللقاح الثلاثي DTP1 وDTP3) عند الأطفال الرضع منخفضي الوزن عند الولادة في غانا، والمحددات المرتبطة بذلك.

الطريقة استخدمنا البيانات المستمدة من تجربة فيتامين ألف التي تستند إلى قطاعات سكانية معينة والتي تم إجراؤها في الفترة من 2010 إلى 2013 على 22 955 رضيع تم تسجيله. أجرينا قياسًا لمعدل تلقي اللقاح والخصائص المتعلقة بالأمهات والأطفال الرضع، كما أجرينا مقارنة بين ثلاث شرائح من الأطفال الرضع منخفضي الوزن عند الولادة (2.0 – 2.4 كلغ؛ و1.5 – 1.9 كلغ؛ والأقل من 1.5 كلغ) من جانب والأطفال الرضع ممن يبلغ وزنهم 2.5 كلغ أو يزيد عن ذلك من جانب آخر. وتم استخدام نموذج التحوف لبواسون لاحتساب نسب معدل تلقي اللقاح بشأن جرعة اللقاح الثلاثي DTP1 عند بلوغ 10 و14 و18 أسبوعًا بعد الولادة، وبشأن جرعة اللقاح الثلاثي DTP3 عند بلوغ 18 و22 و24 أسبوعًا (بما يساوي 1 و2 و3 أشهر بعد مرور 6 و14 أسبوعًا بعد حلول تواريخ وجوب تلقي اللقاحات المذكورة على التوالي).

النتائج كان معدل تلقي جرعة اللقاح الثلاثي DTP1 عند الأطفال الرضع منخفضي الوزن عند الولادة (العدد = 3382) أقل بنسبة تقرب من 40٪ مقارنةً بالأطفال الرضع ممن لا يعانون من انخفاض الوزن عند الولادة (العدد = 18 979)، وذلك في عمر 10 أسابيع (بنسبة المعدل المصححة، aRR: 0.58؛ ونسبة أرجحية مقدارها 95٪: 0.43 – 0.77) وعند بلوغ 18 أسبوعًا (aRR: 0.63؛ ونسبة أرجحية مقدارها 95٪: 0.50–0.80). وكانت معدلات تلقي اللقاح عند الأطفال الرضع ممن يبلغ وزنهم 1.5 – 1.9 (العدد = 386) أقل بنسبة تقرب من 25٪ مقارنةً بالأطفال الرضع ممن يبلغ وزنهم 2.5 كلغ أو أكثر في الأوقات المذكورة. وقد لوحظت نتائج مشابهة لذلك فيما يتعلق بجرعة اللقاح الثلاثي DTP3. وكان ثمة ارتباط بين صغر سن الأمهات، وقصر مدة تعليمهن، وبعد المسافة اللازمة للوصول إلى أقرب

منشأة صحية من جانب وانخفاض معدلات تلقي جرعة اللقاح الثلاثي DTP1 و DTP3 من جانب آخر.
الاستنتاج يمثل الأطفال الرضع منخفضو الوزن عند الولادة مجموعة معرضة لدرجة عالية من الخطر فيما يتعلق بتأخر تلقي اللقاحات اللازمة في غانا. وتقتضي الحاجة بذل الجهود لتعزيز تلقي هؤلاء الأطفال الرضع للقاحات، إلى جانب إجراء المزيد من البحوث لإدراك أسباب التأخر في ذلك.

摘要

加纳农村地区低出生体重婴儿疫苗接种时间：基于群体的前瞻性定群研究

目的 旨在调查加纳低出生体重婴儿在进行第一次和第三次白喉、破伤风、百日咳（DTP1 和 DTP3）疫苗接种时的延误情况和相关因素。
方法 我们所采用的数据来源于 2010-2013 年间在 22 955 名接受调查的婴儿中开展的基于群体的大规模维生素 A 试验。我们衡量了疫苗接种率和母亲及婴儿特征，并将三类低出生体重婴儿（2.0－2.4 公斤；1.5－1.9 公斤；和不足 1.5 公斤）与出生体重大于或等于 2.5 公斤的婴儿相比较，并在出生 10、14 和 18 周后使用泊松回归分析计算 DTP1 疫苗接种率，在 18、22 和 24 周后计算 DTP3 接种率【相当于两个接种截止日期（即 6 周和 14 周）后的第 1、2 和第 3 个月】。
结果 低出生体重婴儿 (n＝3382) 在第 10 周时的 DTP1 接种率大约比非低出生体重婴儿 (n＝18 979) 低 40%（调整后的优势比，aRR: 0.58; 95% CI: 0.43－0.77），第 18 周 (aRR: 0.63; 95% CI: 0.50－0.80)。在所取时间节点，体重在 1.5－1.9 公斤的婴儿 (n＝386) 接种率大约比体重大于或等于 2.5 公斤的婴儿低 25%。DTP3 的观察结果相似。较低的 DTP1 和 DTP3 接种率与孕产年龄较低、受教育程度较低和距离最近的医疗机构较远有关。
结论 低出生体重儿童是加纳接种延迟的高危人群。努力提高这些婴儿的免疫接种率是必要的，同时开展进一步调查，以了解延误原因。

Résumé

Âge de vaccination des nourrissons au faible poids de naissance dans les zones rurales du Ghana: une étude prospective de cohorte menée dans la population

Objectif Examiner les retards d'administration de la première et de la troisième dose de vaccin diphtérie–tétanos–coqueluche (DTP1 et DTP3) chez les nourrissons au faible poids de naissance au Ghana, ainsi que les déterminants associés.
Méthodes Nous avons utilisé les données issues d'un vaste essai sur la vitamine A, mené dans la population en 2010–2013, et qui portait sur 22 955 nourrissons. Nous avons déterminé le taux de vaccination ainsi que les caractéristiques des mères et des enfants et avons comparé trois catégories de nourrissons au faible poids de naissance (2,0–2,4 kg; 1,5–1,9 kg; et < 1,5 kg) avec des nourrissons pesant ≥ 2,5 kg. Une régression de Poisson nous a permis de calculer les ratios des taux de vaccination pour le DTP1 à 10, 14 et 18 semaines après la naissance et, pour le DTP3, à 18, 22 et 24 semaines (ce qui équivaut respectivement à 1, 2 et 3 mois après l'âge normal de vaccination qui est de 6 et 14 semaines).
Résultats Comparés aux nourrissons n'ayant pas un faible poids de naissance (n = 18 979), ceux au faible poids de naissance (n = 3382) avaient un taux de vaccination DTP1 presque 40% plus faible à l'âge de 10 semaines (ratio des taux ajusté, RTa: 0,58; IC 95%: 0,43–0,77) et à l'âge de 18 semaines (RTa: 0,63; IC 95%: 0,50-0,80). Les nourrissons pesant de 1,5 à 1,9 kg (n = 386) avaient un taux de vaccination à ces âges environ 25% plus faible que ceux pesant ≥ 2,5 kg. Des résultats similaires ont été observés pour le DTP3. Le plus jeune âge des mères, leur niveau d'instruction et les distances plus longues jusqu'à l'établissement de soins le plus proche étaient associés à de plus faibles taux de vaccination DTP1 et DTP3.
Conclusion Les nourrissons au faible poids de naissance sont un groupe à haut risque en matière de retard de vaccination au Ghana. Des efforts devraient être entrepris pour améliorer la vaccination de ces enfants, parallèlement à d'autres recherches permettant de comprendre les raisons de ce retard.

Резюме

Сроки проведения вакцинации в сельской местности Ганы для грудных детей со сниженной массой тела при рождении: популяционное проспективное когортное исследование

Цель Изучить несоблюдение сроков первой и третьей вакцинации против дифтерии, коклюша и столбняка (АКДС1 и АКДС3) грудных детей со сниженной массой тела при рождении в Гане и связанные с этим определяющие факторы.
Методы Были использованы данные, полученные в результате обширного популяционного исследования приема витамина А, которое проводилось в 2010–2013 гг. при участии 22 955 грудных детей. Был определен охват вакцинацией матерей и грудных детей, были выявлены их характеристики, и были сопоставлены три категории грудных детей со сниженной (≥2,5 кг) массой тела при рождении: 2,0–2,4; 1,5–1,9 и <1,5 кг. С помощью регрессии Пуассона были подсчитаны отношения рисков вакцинации для вакцинации АКДС1, проведенной на 10, 14 и 18-й неделе после рождения, и для вакцинации АКДС3, проведенной на 18, 22 и 24-й неделе (что соответствует задержке на 1, 2 и 3 месяца по сравнению с установленными сроками такой вакцинации, проводимой на 6-й и 14-й неделях).
Результаты Для младенцев, имевших сниженную массу тела при рождении (n = 3382), охват вакцинацией АКДС1 был приблизительно на 40% ниже по сравнению с остальными младенцами (n = 18 979) в возрасте 10 недель (стандартизированное отношение рисков, СОР: 0,58; 95%-й ДИ: 0,43–0,77) и в возрасте 18 недель (СОР: 0,63; 95%-й ДИ: 0,50–0,80). Охват вакцинацией для младенцев с массой тела

1,5–1,9 кг (n = 386) был приблизительно на 25% ниже, чем для младенцев с массой тела ≥2,5 кг на тот же момент времени. Такие же результаты были получены для АКДС3. Более молодой возраст и меньший уровень образования матери, а также большее расстояние до ближайшего медицинского учреждения коррелировали с меньшим охватом вакцинациями АКДС1 и АКДС3.

Вывод Грудные дети со сниженной массой тела при рождении входят в группу высокого риска несоблюдения сроков вакцинации в Гане. Требуется предпринять меры для повышения охвата вакцинацией этих грудных детей, а также провести дополнительные исследования для понимания причин задержек.

Resumen

Cronograma de vacunación de los recién nacidos con insuficiencia ponderal en la Ghana rural: un estudio poblacional de cohortes prospectivo

Objetivo Investigar los retrasos de la primera y tercera dosis de la vacuna contra la difteria, el tétanos y la tos ferina (DTP1 y DTP3) en recién nacidos con insuficiencia ponderal en Ghana, así como los determinantes relacionados con las mismas.

Métodos En 2010–2013, se utilizaron datos de un ensayo poblacional de vitamina A a gran escala basado en la población con 22 955 recién nacidos inscritos. Se midió la tasa de vacunación y las características tanto de las madres como de los recién nacidos, y se compararon tres categorías de recién nacidos con insuficiencia ponderal (2,0–2,4 kg; 1,5–1,9 kg; y < 1,5 kg) con recién nacidos con un peso de ≥ 2,5 kg. Se utilizaron modelos de regresión de Poisson para calcular los coeficientes de la tasa de vacunación para DTP1 las semanas 10, 14 y 18 después del nacimiento, y para DTP3 las semanas 18, 22 y 24 (lo que equivale a 1, 2 y 3 meses tras las fechas de vencimiento de las vacunaciones correspondiente de las semanas 6 y 14).

Resultados En comparación con los recién nacidos sin insuficiencia ponderal (*n* = 18 979), los que nacieron con bajo peso (*n* = 3 382) tenían una tasa de inmunización sistemática de DTP1 casi un 40% inferior a la edad de 10 semanas (razón de tasa ajustada, aRR: 0,58; IC del 95%: 0,43–0,77) y a la edad de 18 semanas (aRR: 0,63; IC del 95%: 0,50–0,80). Los recién nacidos con un peso de 1,5–1,9 kg (*n* = 386) tenían unas tasas de vacunación de alrededor de un 25% inferior a los que pesaban ≥ 2,5 kg a la misma edad. Para DTP3 se observaron los mismos resultados. Se asociaron la juventud maternal, el bajo nivel educativo y la larga distancia hasta la instalación sanitaria más cercana con las bajas tasas de vacunación de DTP1 y DTP3.

Conclusión Los recién nacidos con insuficiencia ponderal se encuentran en un grupo de alto riesgo para sufrir un retraso de la vacunación en Ghana. Se han garantizado esfuerzos para mejorar la vacunación de estos recién nacidos, junto con una investigación más profunda para comprender las razones de dichos retrasos.

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Table 2. **Birth weight as a determinant of vaccination of infants with first and third doses of diphtheria–tetanus–pertussis vaccine at various ages, rural Ghana, 2010–2013**

Vaccine and age	No. of vaccinations/ no. of person-days of follow-up	Vaccination rate per 100 days of follow-up (95%CI)	Unadjusted RR		aRR[a]		aRR, additionally adjusted for infant illness	
			RR (95% CI)	*P*	aRR (95% CI)	*P*[b]	aRR (95% CI)	*P*
DTP1 at age 10 weeks								
≥ 2.5 kg	14 759/1 065 163	1.39 (1.36–1.41)	Ref	< 0.0001	Ref	< 0.0001	Ref	< 0.0001
2.0–2.4 kg	2 185/166 348	1.31 (1.26–1.37)	0.95 (0.91–0.99)		0.93 (0.89–0.97)		0.93 (0.89–0.97)	
1.5–1.9 kg	243/22 400	1.08 (0.96–1.23)	0.78 (0.69–0.89)		0.71 (0.62–0.81)		0.71 (0.63–0.81)	
< 1.5 kg	45/4 886	0.92 (0.69–1.23)	0.66 (0.50–0.89)		0.58 (0.43–0.77)		0.58 (0.43–0.78)	
DTP1 at age 14 weeks								
≥ 2.5 kg	17 789/1 126 945	1.58 (1.56–1.60)	Ref	0.0064	Ref	< 0.0001	Ref	< 0.0001
2.0–2.4 kg	2680/177 815	1.51 (1.45–1.57)	0.95 (0.92–0.99)		0.92 (0.88–0.96)		0.92 (0.88–0.96)	
1.5–1.9 kg	347/24 482	1.42 (1.28–1.57)	0.90 (0.81–1.00)		0.77 (0.69–0.86)		0.77 (0.69–0.86)	
< 1.5 kg	69/5 497	1.26 (0.99–1.59)	0.80 (0.63–1.01)		0.62 (0.49–0.79)		0.63 (0.49–0.80)	
DTP1 at age 18 weeks								
≥ 2.5 kg	18 427/1 145 653	1.61 (1.59–1.63)	Ref	0.0205	Ref	< 0.0001	Ref	< 0.0001
2.0–2.4 kg	2 810/181 294	1.55 (1.49–1.61)	0.96 (0.93–1.00)		0.92 (0.89–0.96)		0.92 (0.89–0.96)	
1.5–1.9 kg	364/25 020	1.45 (1.31–1.61)	0.90 (0.82–1.00)		0.76 (0.69–0.85)		0.76 (0.69–0.85)	
< 1.5 kg	75/5 708	1.31 (1.05–1.65)	0.82 (0.65–1.02)		0.63 (0.50–0.80)		0.63 (0.50–0.79)	
DTP3 at age 18 weeks								
≥ 2.5 kg	8 007/2 240 325	0.36 (0.35–0.37)	Ref	0.0005	Ref	< 0.0001	Ref	< 0.0001
2.0–2.4 kg	1 168/344 907	0.34 (0.32–0.36)	0.95 (0.89–1.01)		0.93 (0.88–0.99)		0.93 (0.88–0.99)	
1.5–1.9 kg	132/45 006	0.29 (0.25–0.35)	0.82 (0.69–0.97)		0.78 (0.66–0.93)		0.78 (0.66–0.93)	
< 1.5 kg	17/9 381	0.18 (0.11–0.29)	0.51 (0.32–0.82)		0.46 (0.29–0.75)		0.46 (0.29–0.75)	
DTP3 at age 22 weeks								
≥ 2.5 kg	13 238/245 2 731	0.54 (0.53–0.55)	Ref	0.0246	Ref	< 0.0001	Ref	0.0001
2.0–2.4 kg	1 992/378 547	0.53 (0.50–0.55)	0.97 (0.93–1.02)		0.96 (0.91–1.01)		0.96 (0.91–1.01)	
1.5–1.9 kg	239/49 991	0.48 (0.42–0.54)	0.89 (0.78–1.01)		0.80 (0.70–0.92)		0.80 (0.70–0.92)	
< 1.5 kg	41/10 583	0.39 (0.29–0.53)	0.72 (0.53–0.98)		0.61 (0.45–0.83)		0.61 (0.45–0.83)	
DTP3 at age 26 weeks								
≥ 2.5 kg	15 694/2 559 854	0.61 (0.60–0.62)	Ref	0.0334	Ref	< 0.0001	Ref	< 0.0001
2.0–2.4 kg	2 360/395 994	0.60 (0.57–0.62)	0.97 (0.93–1.01)		0.95 (0.91–1.00)		0.95 (0.91–1.00)	
1.5–1.9 kg	296/52 518	0.56 (0.50–0.63)	0.92 (0.82–1.03)		0.82 (0.73–0.92)		0.82 (0.73–0.93)	
< 1.5 kg	51/11 303	0.45 (0.34–0.59)	0.74 (0.56–0.97)		0.60 (0.45–0.79)		0.60 (0.46–0.79)	

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Vaccine and age	No. of vaccinations/ no. of person-days of follow-up	Vaccination rate per 100 days of follow-up (95%CI)	Unadjusted RR		aRR[a]		aRR, additionally adjusted for infant illness	
			RR (95% CI)	*P*	aRR (95% CI)	*P*[b]	aRR (95% CI)	*P*
DTP3 within 12 weeks of DTP1								
≥ 2.5 kg	11 090/375 642	2.95 (2.90–3.01)	Ref	< 0.0001	Ref	0.0026	Ref	0.0069
2.0–2.4 kg	1 664/60 515	2.75 (2.62–2.89)	0.93 (0.88–0.98)		0.93 (0.88–0.98)		0.93 (0.88–0.98)	
1.5–1.9 kg	202/7 548	2.68 (2.33–3.07)	0.91 (0.79–1.04)		0.98 (0.85–1.13)		0.98 (0.85–1.12)	
< 1.5 kg	32/2 330	1.37 (0.97–1.94)	0.47 (0.33–0.66)		0.65 (0.46–0.92)		0.65 (0.46–0.93)	

aRR: adjusted rate ratio; CI: confidence interval; DTP1: first dose of diphtheria–tetanus–pertussis vaccine; DTP3: third dose of diphtheria–tetanus–pertussis vaccine; Ref: reference group; RR: rate ratio.

[a] Adjusted for ethnicity, religion, socioeconomic status, maternal occupation, maternal education, season when vaccine due, infant sex, maternal age, family size, maternal illness in year before delivery, distance from health facility, place of delivery, multiple birth and age-band of infant.

[b] *P*-value for linear trend.

Table 3. **Determinants of delayed vaccination with first dose diphtheria–tetanus–pertussis vaccine at age 10 weeks and third dose diphtheria–tetanus–pertussis vaccine at age 18 weeks for infants, rural Ghana, 2010–2013**

Determinants	DTP1 at age 10 weeks				DTP3 at age 18 weeks			
	Unadjusted RR		aRR[a]		Unadjusted RR		aRR[a]	
	RR (95% CI)	*P*	aRR (95% CI)	*P*	RR (95% CI)	*P*	aRR (95% CI)	*P*
Distal determinants								
Religion of head of household								
Christian	Ref	0.0002	Ref	0.0382	Ref	< 0.0001	Ref	< 0.0001
Muslim	0.93 (0.90–0.97)		0.95 (0.91–0.99)		0.77 (0.73–0.81)		0.81 (0.77–0.86)	
None/traditional/other	0.94 (0.88–1.00)		0.99 (0.93–1.06)		0.93 (0.86–1.01)		1.01 (0.93–1.10)	
Ethnicity of household								
Akan	Ref	< 0.0001	Ref	0.0728	Ref	< 0.0001	Ref	0.3484
Other	0.94 (0.91–0.96)		1.04 (1.00–1.08)		0.85 (0.82–0.89)		1.03 (0.97–1.08)	
Socioeconomic status								
1 (poorest)	0.84 (0.80–0.88)	< 0.0001	0.96 (0.90–1.02)	0.5398	0.87 (0.81–0.93)	0.0001	1.13 (1.04–1.23)	0.0010
2	0.91 (0.87–0.95)		1.00 (0.94–1.05)		0.95 (0.89–1.02)		1.15 (1.07–1.24)	
3	0.93 (0.89–0.97)		0.98 (0.93–1.03)		1.00 (0.94–1.06)		1.13 (1.06–1.21)	
4	0.95 (0.91–1.00)		0.98 (0.94–1.03)		0.97 (0.91–1.03)		1.05 (0.99–1.12)	
5 (richest)	Ref		Ref		Ref		Ref	
Maternal occupation								
Government/private/other	1.08 (1.01–1.16)	< 0.0001	1.09 (1.02–1.17)	0.0031	1.16 (1.06–1.27)	0.0013	1.11 (1.01–1.21)	0.0394
Self-employed	Ref		Ref		Ref		Ref	
Farming	0.90 (0.87–0.94)		0.95 (0.91–0.99)		0.96 (0.92–1.01)		1.07 (1.00–1.13)	
Not working	0.95 (0.92–0.99)		0.99 (0.95–1.03)		0.99 (0.94–1.04)		1.05 (0.99–1.11)	
Maternal education								
None	0.88 (0.85–0.91)	< 0.0001	0.88 (0.84–0.92)	< 0.0001	0.77 (0.73–0.81)	< 0.0001	0.77 (0.72–0.81)	< 0.0001
Primary school	0.93 (0.89–0.96)		0.93 (0.89–0.97)		0.84 (0.80–0.89)		0.85 (0.80–0.90)	
Secondary/tertiary	Ref		Ref		Ref		Ref	
Season when vaccine due								
Wet	Ref	0.2971	Ref	0.1817	Ref	0.0480	Ref	0.0511
Dry	0.98 (0.95–1.01)		0.98 (0.95–1.01)		0.96 (0.92–1.00)		0.96 (0.92–1.00)	
Infant sex								
Male	Ref	0.5352	Ref	0.2206	Ref	0.2602	Ref	0.1165
Female	1.01 (0.98–1.04)		1.02 (0.99–1.05)		1.02 (0.98–1.07)		1.03 (0.99–1.08)	

(*continues. . .*)

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Determinants	DTP1 at age 10 weeks				DTP3 at age 18 weeks			
	Unadjusted RR		aRR[a]		Unadjusted RR		aRR[a]	
	RR (95% CI)	*P*	aRR (95% CI)	*P*	RR (95% CI)	*P*	aRR (95% CI)	*P*
Intermediate determinants								
Maternal age, years								
< 20	0.90 (0.86–0.95)	0.0053	0.84 (0.78–0.89)	< 0.0001	0.87 (0.80–0.93)	0.0030	0.77 (0.70–0.84)	< 0.0001
20–24	0.97 (0.93–1.01)		0.93 (0.89–0.98)		0.97 (0.92–1.03)		0.93 (0.88–0.99)	
25–29	Ref		Ref		Ref		Ref	
30–34	0.98 (0.94–1.02)		1.03 (0.98–1.07)		0.99 (0.93–1.05)		1.06 (0.99–1.13)	
≥ 35	0.96 (0.91–1.00)		1.02 (0.97–1.08)		0.96 (0.90–1.02)		1.06 (0.99–1.14)	
No. of children in family								
0–1	1.00 (0.96–1.03)	0.0103	1.05 (1.00–1.10)	0.0066	1.00 (0.95–1.05)	0.0039	1.07 (1.01–1.13)	0.0004
2–3	Ref		Ref		Ref		Ref	
≥ 4	0.95 (0.92–0.98)		0.95 (0.91–1.00)		0.93 (0.88–0.97)		0.92 (0.86–0.97)	
Maternal illness								
No	Ref	0.4939	Ref	0.1319	Ref	0.9296	Ref	0.7234
Yes	1.02 (0.96–1.10)		1.05 (0.98–1.13)		1.00 (0.91–1.09)		1.02 (0.93–1.12)	
Distance from health facility (km)								
< 1.0	Ref	< 0.0001	Ref	< 0.0001	Ref	< 0.0001	Ref	< 0.0001
1.0–4.9	0.95 (0.92–0.99)		0.94 (0.90–0.97)		0.93 (0.88–0.98)		0.90 (0.86–0.95)	
≥ 5.0	0.85 (0.81–0.89)		0.86 (0.82–0.91)		0.78 (0.73–0.83)		0.79 (0.74–0.84)	
Place of birth								
Health facility	Ref	< 0.0001	Ref	0.0065	Ref	< 0.0001	Ref	0.0281
Non-facility	0.89 (0.86–0.92)		0.94 (0.91–0.98)		0.86 (0.82–0.91)		0.94 (0.89–0.99)	
Multiple birth								
No	Ref	0.1420	Ref	0.4172	Ref	0.8390	Ref	0.1225
Yes	0.94 (0.87–1.02)		1.04 (0.95–1.13)		0.99 (0.89–1.10)		1.10 (0.98–1.24)	
Mediating variables								
Infant illness								
No	Ref	0.0507	Ref	0.0949	Ref	0.1540	Ref	0.2632
Yes	0.96 (0.91–1.00)		0.95 (0.91–1.00)		0.96 (0.91–1.02)		1.02 (0.96–1.08)	

aRR: adjusted rate ratio; CI: confidence interval; DTP1: first dose of diphtheria–tetanus–pertussis vaccine; DTP3: third dose of diphtheria–tetanus–pertussis vaccine; Ref: reference group; RR: rate ratio.

[a] Also adjusted for infant age-band.

5.3. CONSIDERATIONS INFLUENCING THE STUDY DESIGN

As discussed in **Chapter 1**, standard reporting of vaccine uptake at 52 weeks of age does not capture uptake rates among infants who die before reaching 52 weeks of age and who may be more likely to be under-vaccinated. These infants may also be more likely to be LBW. Similarly, any effect of birth weight on vaccination rate may be most apparent earlier in life, before LBW babies have had a chance to catch up with their growth.

As uptake rates among LBW infants are not routinely reported, there are no recommendations on appropriate indicator vaccines that could facilitate an assessment of their vaccination status and that would capture lower rates of vaccination among LBW infants. For this group of infants, an earlier indicator of uptake may be more appropriate.

5.3.1. Selection of DTP1 and DTP3 as indicator vaccines

With the above issues in mind, I chose to use DTP1 and DTP3 vaccines as indicator vaccines for adherence to the routine infant vaccination schedule. Both DTP1 and DTP3 are scheduled to be given relatively early in life, with DTP1 scheduled at 6 weeks of age, and DTP3 at 14 weeks of age. I therefore reasoned that these vaccines would be good indicators for assessing any effect of birth weight on adherence to the schedule. I decided to analyse time to vaccination rather than uptake at specific ages, so that so all infants would contribute person-time for as long as they were in follow-up, and so that I could maximise the inclusion of infants (including LBW infants) in the analyses. In addition, DTP3 is one of the most commonly reported indicators in vaccine programme evaluation. By investigating DTP3 vaccination, I was able to relate my findings to other published data.

5.3.2. Defining the risk periods for the analyses

Given the changing nature of both infant weight and vaccination uptake over time, the choice of time-point for measuring delayed vaccination was critical in order to capture the effect of fragility associated with birth weight. Consequently, I chose to measure time to vaccination at a number of progressively later time points (four, eight and twelve weeks after the due date for vaccination). The selection of these time points was justified for a number of reasons. A vaccination delay of 12 weeks or more after the due date is very late for the administration of a vaccine, and represents a noteworthy deviation from the schedule. Furthermore, WHO recommends that the full DTP schedule be completed by six months of age in areas where pertussis is especially a risk to young infants[28]. A 12-week delay in the administration of either DTP1 or DTP3 would result in an infant not completing

the DTP schedule by this time point. Finally, as well as being sensitive time-points to capture any effect of birth weight, this approach also allowed me to consider the changing effect of birth weight on vaccination over time.

5.4. CONSIDERATIONS IN THE CHOICE OF ANALYTICAL METHODOLOGY

As discussed in **Section 1.5.4**, LBW infants were expected to have higher rates of mortality, and this was confirmed in the analyses reported in **Chapter 4**.

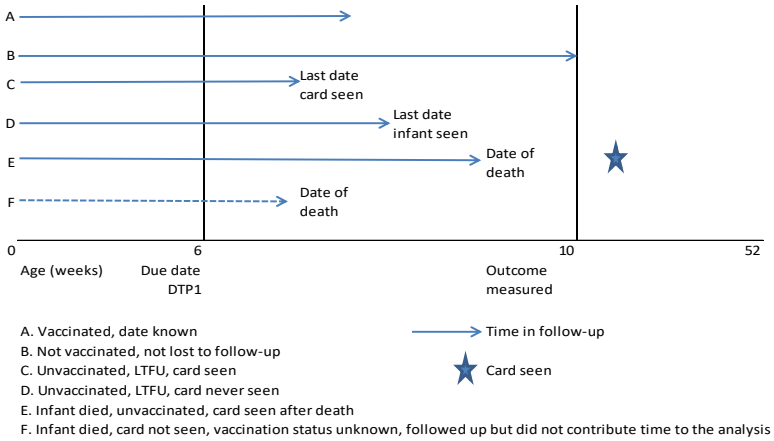
As mentioned above, my outcomes for these analyses (vaccination with DTP1 and DTP3) were likely to vary over time. I generated Kaplan Meier curves of time to vaccination to describe and compare the probability of vaccination among LBW and NLBW infants over time. Cox regression is a commonly used approach for regression analysis of time-varying outcome data, particularly outcomes that vary rapidly over time. Although vaccination does vary over time, I did not expect the rate to change so rapidly within the time-periods of interest (up to 12 weeks after the vaccine due date) to necessitate the use of Cox regression. Cox regression does not allow for the estimation of underlying rates, and for this reason, I opted to use Poisson regression to calculate adjusted vaccination rate ratios of the association between birth weight and vaccination, and for the investigation of other determinants of vaccination. I split the follow-up time into one month intervals to create a time variable, and I included this time-variable in all of the multivariable models to adjust for variations in vaccination rate by infant-age. I used a causal modelling approach to model building, as described in **Section 3.7.3**. I repeated the analysis of the final multivariable model using Cox regression. There was little difference in the effect estimates generated by Poisson and Cox regression (**Table A5.1, Appendix 5.1**).

5.5. DID THE CATEGORISATION OF INFANTS BY VACCINATION STATUS BIAS THE ESTIMATES OF ASSOCIATION?

As explained in the paper, in these analyses, I defined the end of follow up as the vaccination date for vaccinated infants, and the end of the risk period for unvaccinated infants not lost-to-follow-up. For those lost-to-follow-up before the end of the risk period, I defined the end of follow-up as a) the last date the written record was viewed for unvaccinated infants whose record was viewed, b) the last date the infant was seen for unvaccinated infants whose record was never viewed or c) the date of death for unvaccinated infants who died before the end of the risk period and whose record was

viewed after their death. An illustrated example for DTP1 vaccination is given (**Figure 5.1**). Infants with unknown vaccination status did not contribute any follow-up time to the analyses.

Figure 5.1: Defining the follow-up period for the analysis of time to DTP1 vaccination, based on vaccination status & duration of follow-up



Throughout the first year of life LBW infants were consistently over-represented among infants who died (**Table 5.1**).

Table 5.1: Percentage of LBW and NLBW infants who died per month

	Deaths[1]	
Age in Days	**LBW n/N (%)[2]**	**Non-LBW n/N (%)[3]**
0-27	137/3440 (3.8)	150/19141 (0.8)
28-59	33/3400 (4.8)	54/19054 (1.1)
60-89	10/3381 (5.0)	24/18997 (1.2)
90-119	14/3359 (5.4)	28/18936 (1.3)
120-149	15/3329 (5.9)	19 (18893 (1.4)
150-179	15/3311 (6.3)	26/18827 (1.6)
180-209	6/3294 (6.5)	29/18772 (1.7)
210-239	7/3275 (6.7)	26/18704 (1.9)
240-269	10/3254 (6.9)	26/18639 (2.0)
270-299	6/3240 (7.1)	13/18583 (2.1)
300-329	8/3222 (7.3)	24/18494 (2.2)
330-365	4/3196 (7.5)	14/18377 (2.3)

1. one death with unknown birth weight
2. % of all LBW infants
3 % of all NLBW infants

As explained in **Section 5.4**, the use of Poisson regression allowed me to maximize the retention of infants who died and who had a known vaccination status in my analyses, thus minimizing any bias associated with the excess rates of mortality among these LBW infants. However, using DTP1 as an example, it is evident that infants who died were also more likely

to be categorised as vaccination status unknown (**Table 5.2**), and therefore to be excluded from the analyses.

Overall, 46% (323/699) of infants who died in the first year of life died before they were eligible for vaccination. These infants were not included in the analysis. Of the 323 who died before they were eligible for vaccination, most (215, 67%) were vaccination status unknown (**Table 5.2**).

Table 5.2: DTP1 vaccination status by vital status and follow-up status

		Vaccination Status				
	A. Total	**Card seen, vaccinated, date known**	**Card seen, date unknown, vaccination date imputed**	**Card seen, known not vaccinated**	**Reported as not vaccinated, card not seen**	**Status unknown (% of A. total)**
All infants	22955	22104	33	288	125	404 (1.8)
Live infants	22256	21805	33	181	58	179 (0.8)
Died (all)	699	299	0	107	67	226 (32)
Died < 6 weeks	323	1	0	56	51	215 (67)
Died 6-10 weeks	59	9	0	32	11	7 (12)
Died 6-14 weeks	97	38	0	41	11	7 (7)
Died 6-18 weeks	**134**	**68**	**0**	**46**	**12**	**8 (6)**
LTFU < 6 weeks	615	9	0	77	125	404 (66)
LTFU 6-10 weeks	169	65	0	104	0	0 (0)
LTFU 6-14 weeks	348[1]	213	1	134	0	0 (0)
LTFU 6-18 weeks	522[1]	374	1	147	0	0 (0)

Discounting these ineligible infants, the number of infants who died in the risk periods used for the DTP1 analyses were small. For example, 134 infants (0.6% of all enrolled infants) died between 6 and 18 weeks of age (**Table 5.2**). A further 179 infants who did not die (0.8% of all enrolled infants) were also vaccination status unknown (**Table 5.2**). Given the small numbers involved, the fact that LBW infants were more likely to die and were more likely to be categorised as vaccination status unknown is unlikely to have had any great impact on the generalisability of the results.

5.6. DID INCLUDING INFANTS WITH MISSING VACCINATION CARDS BIAS THE ESTIMATES OF THE ASSOCIATION BETWEEN BIRTH WEIGHT AND VACCINATION?

As discussed in **Section 3.2**, I categorised infants whose vaccination card was never seen, and who were consistently reported as never having been vaccinated, as not vaccinated. This was to maximise the inclusion of infants who were never issued a vaccination card simply because they never attended child health or vaccination clinics. As the categorisation of these infants was based on maternal recall, their vaccination status may have been misclassified due to poor maternal recall. If this misclassification were differential by birth weight, this may have biased the estimates of the association between birth weight and vaccination. As shown in **Table 5.3** the numbers in this category were very small (<1% for all vaccines), and so they were unlikely to have greatly influenced the effect estimates in the analyses of vaccination status.

Table 5.3: Infant vaccination status for each vaccine included in the routine vaccination programme

	Category of Vaccination Status N (% of all enrolled infants)				
Vaccine	**Card seen, vaccinated, date known**	**Card seen, vaccinated, date unknown**	**Card seen, known not vaccinated**	**Card not seen, not vaccinated**	**Status unknown**
BCG	22002 (95.8)	243 (1.1)	348 (1.5)	0 (0.0)	362 (1.6)
Birth OPV	14831 (64.6)	487 (2.1)	6699 (29.2)	0 (0.0)	938 (4.1)
OPV1	21739 (94.7)	80 (0.3)	603 (2.6)	127 (0.6)	406 (1.8)
OPV2	21583 (94.0)	48 (0.2)	791 (3.4)	127 (0.6)	406 (1.8)
OPV3	20644 (89.9)	167 (0.7)	1611 (7.0)	127 (0.6)	406 (1.8)
DTP1	22105 (96.3)	27 (0.1)	291 (1.2)	130 (0.6)	402 (1.8)
DTP2	21698 (94.5)	17 (0.1)	708 (3.1)	127 (0.5)	405 (1.8)
DTP3	21099 (91.9)	38 (0.2)	1282 (5.6)	123 (0.5)	413 (1.8)
Measles	18472 (80.5)	58 (0.3)	3247 (14.1)	0 (0.0)	1178 (5.1)
Yellow Fever	18402 (80.2)	93 (0.4)	4009 (17.5)	101 (0.4)	350 (1.5)

In order to further explore whether this categorisation had biased the estimates, for the analyses of DTP1 and DTP3 vaccination at 12 weeks after the vaccine due date, I undertook additional sensitivity analyses (**Appendix 5.1**, **Table A5.2 and A5.3** (at the end of **Chapter 5**), whereby I also excluded these infants. **Table 5.4** presents the effect estimates in the final model (adjusted for distal, intermediate and proximate determinants, and the mediating effect of infant illness), in models including and excluding these infants. It can be

seen that excluding these infants made little difference to the size of the effect estimates, indicating that their inclusion in the analyses did not bias the estimates.

Table 5.4. Comparison of estimated effect of determinants of DTP1 and DTP3 vaccination, including (A) and excluding (B) infants reported not vaccinated but whose card was never seen.

	DTP1 between 0 and 18 weeks		DTP3 between 0 and 26 weeks	
	A	B	A	B
	Rate Ratios[1] aRR (95%CI)	Rate Ratios[1] aRR (95%CI)	Rate Ratios[1] aRR (95%CI)	Rate Ratios[1] aRR (95%CI)
Distal Determinants				
Religion				
Christian	ref	*ref*	ref	ref
Muslim	0.92 (0.89-0.95)	0.93 (0.89-0.96)	0.82 (0.79-0.85)	0.82 (0.79-0.86)
None/Traditional/ Other	0.96 (0.90-1.01)	0.95 (0.90-1.01)	0.94 (0.88-1.00)	0.93 (0.88-0.99)
	(<0.0001)	(0.0001)	(<0.0001)	(<0.0001)
Ethnicity of household	ref	*ref*	ref	ref
Akan	1.03 (0.99-1.06)	1.02 (0.98-1.05)	0.97 (0.94-1.01)	0.97 (0.93-1.01)
Other	(0.1196)	(0.2996)	(0.1889)	(0.1172)
Socioeconomic status	0.94 (0.89-0.99)	0.96 (0.91-1.01)	1.09 (1.03-1.16)	1.10 (1.04-1.17)
1 (poorest)	0.99 (0.95-1.04)	1.01 (0.96-1.05)	1.14 (1.08-1.20)	1.15 (1.09-1.21)
2	0.99 (0.95-1.04)	1.00 (0.96-1.04)	1.11 (1.05-1.16)	1.11 (1.06-1.16)
3	0.99 (0.95-1.03)	0.99 (0.95-1.03)	1.06 (1.01-1.11)	1.06 (1.01-1.11)
4	ref	*ref*	Ref	ref
5 (richest)	(0.1676)	(0.2478)	(0.0001)	(<0.0001)
Maternal occupation				
Gov/Private/Other	1.08 (1.01-1.15)	1.08 (1.01-1.15)	1.07 (1.01-1.15)	1.08 (1.01-1.15)
Self-employed	ref	*ref*	ref	ref
Farming	0.97 (0.93-1.01)	0.96 (0.93-1.00)	1.09 (1.04-1.13)	1.09 (1.04-1.13)
Does not work	0.99 (0.96-1.03)	0.99 (0.96-1.03)	1.02 (0.98-1.06)	1.02 (0.98-1.07)
	(0.0229)	(0.0179)	(0.0006)	(0.0006)
Maternal education				
None	0.88 (0.84-0.91)	0.88 (0.85-0.92)	0.78 (0.75-0.82)	0.78 (0.75-0.82)
Primary school	0.93 (0.89-0.96)	0.93 (0.89-0.96)	0.83 (0.80-0.87)	0.83 (0.80-0.87)
Secondary / tertiary	ref	*ref*	ref	ref
	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
Season vaccine due				
Wet	ref	*ref*	ref	ref
Dry	1.00 (0.97-1.02)	0.99 (0.97-1.02)	0.96 (0.92-0.98)	0.95 (0.92-0.98)
	(0.7494)	(0.6030)	(0.0002)	(0.0003)

Continued….

Table 5.4 continued

	DTP1 between 0 and 18 weeks		DTP3 between 0 and 26 weeks	
	A	B	A	B
	Rate Ratios[1] aRR (95%CI)	Rate Ratios[1] aRR (95%CI)	Rate Ratios[1] aRR (95%CI)	Rate Ratios[1] aRR (95%CI)
Sex				
Male	ref	*ref*	ref	ref
Female	1.02 (1.00-1.05) (0.0804)	1.02 (0.99-1.05) (0.1714)	1.04 (1.01-1.07) (0.0191)	1.03 (1.00-1.06) (0.0304)
Intermediate Determinants				
Maternal age (years)				
15 – 19	0.84 (0.79-0.89)	0.84 (0.79-0.89)	0.80 (0.75-0.85)	0.80 (0.75-0.85)
20 – 24	0.93 (0.89-0.97)	0.93 (0.89-0.97)	0.91 (0.87-0.95)	0.90 (0.87-0.94)
25 – 29	ref	*ref*	ref	ref
30 – 34	1.02 (0.98-1.07)	1.03 (0.99-1.07)	1.07 (1.02-1.12)	1.07 (1.02-1.12)
35 years and over	1.02 (0.97-1.07) (<0.0001)	1.02 (0.97-1.07) (<0.0001)	1.06 (1.01-1.12) (<0.0001)	1.06 (1.01-1.12) (<0.0001)
Number of living children in family				
0-1	1.05 (1.01-1.09)	1.05 (1.01-1.09)	1.07 (1.03-1.12)	1.07 (1.03-1.12)
2-3	ref	*ref*	ref	ref
4 or more	0.95 (0.91-0.99) (0.0007)	0.95 (0.91-0.99) (0.0008)	0.88 (0.85-0.92) (<0.0001)	0.88 (0.84-0.92) (<0.0001)
Maternal illness				
No	ref	*ref*	ref	ref
Yes	1.03 (0.97-1.10) (0.2998)	1.03 (0.97-1.09) (0.4033)	0.98 (0.92-1.05) 0.6288	0.98 (0.92-1.05) (0.5719)
Distance from health facility				
<1.00km	ref	*ref*	ref	ref
1.00-4.99km	0.96 (0.93-0.99)	0.96 (0.93-0.99)	0.98 (0.95-1.02)	0.98 (0.95-1.02)
>=5.00km	0.87 (0.83-0.91) (<0.0001)	0.87 (0.84-0.91) (<0.0001)	0.81 (0.77-0.85) (<0.0001)	0.81 (0.78-0.85) (<0.0001)
Place of birth				
Facility	ref	*ref*	ref	ref
Non-facility	0.94 (0.91-0.98) (0.0011)	0.94 (0.91-0.98) (0.0012)	0.95 (0.91-0.99) (0.0120)	0.95 (0.91-0.99) (0.0120)
Multiple birth				
No	ref	*ref*	ref	ref
Yes	1.08 (1.00-1.17) (0.0539)	1.08 (1.00-1.17) (0.0473)	1.07 (0.98-1.16) (0.1298)	1.07 (0.98-1.17) (0.1197)
Distal Determinants				
Birth weight				
>=2.5kg	ref	*ref*	ref	ref
2.00-2.49kg	0.92 (0.89-0.96)	0.92 (0.89-0.96)	0.95 (0.91-1.00)	0.95 (0.91-1.00)
1.50-1.99kg	0.77 (0.69-0.85)	0.76 (0.69-0.85)	0.82 (0.73-0.92)	0.82 (0.73-0.92)
<1.50kg	0.64 (0.51-0.80) (<0.0001)	0.63 (0.50-0.79) (<0.0001)	0.60 (0.46-0.79) (<0.0001)	0.60 (0.45-0.79) (<0.0001)
Mediating Variables				
Infant illness				
No	ref	*ref*	ref	ref
Yes	0.94 (0.90-0.98) (0.0028)	0.95 (0.91-0.99) (0.0039)	1.03 (0.99-1.07) (0.1498)	1.02 (0.98-1.07) (0.1151)

1. Effect estimates adjusted for infant age-band, for distal, intermediate and proximal variables, and for the mediating effects of infant illness.

5.7. ADDITIONAL RESULTS AND DISCUSSION

In this section, I present additional tables of results not included in the published paper and I discuss these results.

5.7.1: How does vaccine uptake by birth weight in the Neovita study population relate to international targets?

Table 5.5 summarises the monthly DTP1 and DTP3 uptake rates by birth weight among infants included in my analyses. This table clearly illustrates delayed vaccination in our entire study population, as well as declining uptake with declining birth weight for both DTP1 and DTP3. For DTP1, ≥90% uptake (the target stipulated in the current Global Vaccine Action Plan[1]) was achieved for all categories of birth weight by age 17 weeks (120 days), 11 weeks after the DTP1 due date. For DTP3, it took substantively longer for infants to reach this target. For NLBW infants, and infants weighing 2.00-2.49kg, this target was only reached by 16 weeks after the vaccine due date (at 210 days / 30 weeks of age), MLBW infants reached the target 20 weeks after the vaccine due date (at 240 days / 34 weeks of age). For VLBW infants, it took an additional 29 weeks beyond the due date (until 300 days / 43 weeks of age) to meet this target.

5.7.2: How do the reported estimates of vaccine uptake in the Neovita study population relate to other published estimates for Ghana?

The estimated 99% DTP1 uptake at 52 weeks of age for all categories of birth weight (**Table 5.5)** is higher than officially reported WHO/UNICEF estimates for Ghana during the study period (94% for 2011 and 92% for 2012)[2], but is equal to that reported in a previous analysis of vaccination in the study area using data on infants born in 2008 and 2009[3].

The DTP3 uptake rates, which were in excess of 97% for all infants except those weighing <1.50kg were higher than the 91% and 92% uptake rates reported by WHO/UNICEF[2] and were slightly higher than the 94% uptake previously reported in the study area[3]. The slightly higher uptake rates in my analyses may reflect 1) the better health outcomes in the Brong Ahafo region as compared to Ghana as a whole (as discussed in **Chapter 2**), 2) the fact that this was a trial population who were being reminded on a monthly basis about vaccination (as discussed in the paper), and 3) improvements to the delivery of vaccines in the study area over time.

Table 5.5: Monthly uptake rates by birth weight for a) DTP1 and b) DTP3

	% uptake DTP1			
Uptake by	**Non-LBW (95%CI)**	**2.49-2.00 kg (95%CI)**	**1.99-1.5kg (95%CI)**	**<1.5kg (95%CI)**
Day 30	0.6 (0.5-0.7)	0.6 (0.4-0.9)	0.3 (0.0-1.8)	0.0 (0.0-0.0)
Day 42	***8.5 (8.1-8.9)***	***7.5 (6.6-8.5)***	***8.9 (6.4-12.2)***	***2.5 (0.6-9.6)***
Day 60	60.2 (59.5-60.9)	56.0 (54.2-57.8)	50.6 (45.7-55.7)	40.0 (30.2-51.6)
Day 70	***79.6 (79.0-80.2)***	***76.3 (74.7-77.8)***	***67.3 (62.6-72.0)***	***58.8 (48.3-69.6)***
Day 90	92.2 (91.8-92.6)	90.2 (89.0-91.2)	87.0 (83.4-90.1)	81.3 (72.0-88.9)
Day 98	***94.5 (94.2-94.8)***	***92.9 (91.9-93.8)***	***92.3 (89.3-94.7)***	***87.5 (79.3-93.6)***
Day 120	97.4 (97.2-97.6)	96.8 (96.1-97.4)	95.8 (93.4-97.5)	93.8 (87.0-97.7)
Day 126	***97.8 (97.6-98.0)***	***97.3 (96.6-97.8)***	***96.8 (94.7-98.3)***	***93.8 (87.0-97.7)***
Day 150	98.7 (98.5-98.8)	98.4 (97.9-98.8)	98.4 (96.7-99.3)	95.0 (88.7-98.4)
Day 180	99.2 (99.0-99.3)	98.9 (98.5-99.2)	98.7 (97.1-99.5)	96.3 (90.4-99.0)
Day 210	99.3 (99.2-99.4)	99.0 (98.6-99.4)	98.7 (97.1-99.5)	96.3 (90.4-99.0)
Day 240	99.4 (99.3-99.5)	99.1 (98.8-99.4)	99.0 (97.5-99.7)	98.8 (94.0-99.9)
Day 270	99.5 (99.3-99.6)	99.2 (98.8-99.5)	99.0 (97.5-99.7)	98.8 (94.0-99.9)
Day 300	99.5 (99.4-99.6)	99.3 (98.9-99.6)	99.0 (97.5-99.7)	98.8 (94.0-99.9)
Day 330	99.5 (99.4-99.6)	99.3 (99.0-99.6)	99.7 (98.4-100.0)	98.8 (94.0-99.9)
Day 365	99.5 (99.4-99.6)	99.3 (99.0-99.6)	99.7 (98.4-100.0)	98.8 (94.0-99.9)
	% uptake DTP3			
Uptake by	**Non-LBW (95%CI)**	**2.49-2.00 kg (95%CI)**	**1.99-1.5kg (95%CI)**	**<1.5kg (95%CI)**
Day 30	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Day 60	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Day 90	0.3 (0.3-0.4)	0.2 (0.1-0.5)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Day 98	***2.0 (1.8-2.2)***	***1.7 (1.3-2.3)***	***2.7 (1.5-4.9)***	***0.0 (0.0-0.0)***
Day 120	35.2 (34.5-35.9)	32.5 (30.8-34.3)	29.9 (25.5-34.9)	18.9 (11.7-29.8)
Day 126	***44.6 (43.9-45.4)***	***43.2 (41.4-45.0)***	***36.8 (32.1-41.9)***	***23.1 (15.0-34.5)***
Day 150	69.3 (68.6-70.0)	67.8 (66.1-69.5)	63.4 (58.4-68.3)	55.3 (44.3-66.9)
Day 154	***72.2 (71.6-72.9)***	***71.0 (69.3-72.6)***	***66.5 (61.6-71.3)***	***56.7 (45.6-68.2)***
Day 180	84.6 (84.1-85.2)	83.1 (81.7-84.5)	81.7 (77.5-85.5)	70.8 (60.0-80.8)
Day 182	***85.3 (84.7-85.8)***	***84.0 (82.6-85.3)***	***81.9 (77.8-85.7)***	***72.2 (61.6-82.0)***
Day 210	91.3 (90.8-91.7)	90.4 (89.2-91.4)	89.3 (85.8-92.2)	78.1 (67.9-86.9)
Day 240	94.3 (93.9-94.6)	93.6 (92.6-94.5)	91.9 (88.8-94.5)	81.0 (71.1-89.2)
Day 270	95.8 (95.5-96.1)	95.1 (94.2-95.8)	95.1 (92.5-97.0)	87.3 (78.2-93.9)
Day 300	96.5 (96.3-96.8)	95.9 (95.1-96.6)	96.5 (94.2-98.1)	90.5 (82.0-96.0)
Day 330	97.0 (96.7-97.2)	96.7 (95.9-97.3)	97.7 (95.7-98.9)	92.1 (84.0-97.0)
Day 365	97.4 (97.1-97.6)	97.1 (96.3-97.7)	98.1 (96.1-99.2)	93.7 (86.0-97.9)

5.7.3. Mediation of the observed effects by more proximal variables.

Table 5.6 presents detailed results for the hierarchical modelling of DTP1 vaccination between 0 and 10 weeks of age (unadjusted and fully adjusted estimates presented in Table 3 of the published paper). Detailed results for the hierarchical modelling of DTP1 vaccination between 0 and 14 weeks, and 0 and 18 weeks are given in **Appendix 5.1 (Tables A5.4 and A5.5)**. With the exception of SES, there was little evidence of mediation of distal level factors by intermediate factors, or that either distal or intermediate factors were mediated by birth weight or infant illness. For SES, DTP1 vaccination by each of 10 and 14 weeks of age was, in distal models, observed to be up to 15% lower amongst the poorest

quintile. This association was no longer observed once adjusted for the intermediate variables, suggesting that it was largely explained by intermediate factors such as maternal age and distance to the nearest health facility.

Similarly, for DTP3 (**Table 5.7 and Appendix 5.1, Tables A5.6 and A5.7**), there was little evidence of mediation of any variables by other more proximal factors. Again, the only exception to this was for SES. At up to 18 weeks of age (4 weeks after the vaccine due date) (**Table 5.7**), the evidence of an association with vaccination was weak in distal models, but evidence of an association increased once adjusted for the intermediate variables. A small association was consistently observed across all models at 8 and 12 weeks after the vaccine due date, whereby infants in the lower categories of deprivation had a moderately (<20%) increased vaccination rate compared to those in the highest category. This association may be an artefact of delayed receipt of DTP1, as will be further discussed in **Section 5.7.4.**

Table 5.6: Determinants of DTP1 vaccination between age 0 and 10 weeks

	Vaccinations / Person days of follow-up	Vaccination Rate / 100 days of follow-up	Unadjusted Rate Ratios RR (95%CI) (p-value)	Rate Ratios adjusted for age-band* aRR (95%CI) (p-value)	Rate Ratios adjusted for distal determinants aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants and birth weight aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants and birth weight and illness aRR (95%CI) (p-value)
Infant age-band (in days)								
<29.5	130/670092	0.02 (0.02-0.02)	0.01 (0.01-0.01)		0.01 (0.01-0.01)	0.01 (0.01-0.01)	0.01 (0.01-0.01)	0.01 (0.01-0.01)
29.5-60.0	13098/524434	2.50 (2.46-2.54)	ref	_	ref	ref	ref	ref
>90.0	4004/642711	6.23 (6.04-6.43)	2.49 (2.41-2.58) (<0.0001)	_	2.52 (2.44-2.61) (<0.0001)	2.54 (2.45-2.63) (<0.0001)	2.55 (2.46-2.64) (<0.0001)	2.55 (2.46-2.64) (<0.0001)
Distal Determinants								
Religion of head of household								
Christian	12242/876372	1.40 (1.37-1.42)	ref	ref	ref	ref	ref	ref
Muslim	3933/301612	1.30 (1.26-1.35)	0.93 (0.90-0.97)	0.91 (0.88-0.95)	0.94 (0.90-0.98)	0.95 (0.91-0.99)	0.95 (0.91-0.99)	0.95 (0.91-0.99)
None/Traditional/Other	1057/80813	1.31 (1.23-1.39)	0.94 (0.88-1.00) (0.0002)	0.90 (0.85-0.96)	0.98 (0.92-1.04) (0.0196)	0.99 (0.93-1.06) (0.0371)	0.99 (0.93-1.06) (0.0357)	0.99 (0.93-1.06) (0.0382)
Ethnicity of household								
Akan								
Other	8331/587695	1.42 (1.39-1.45)	ref	ref	ref	ref	ref	ref
	8901/671102	1.33 (1.30-1.35)	0.94 (0.91-0.96) (<0.0001)	0.92 (0.89-0.95)	1.04 (1.00-1.08) (0.0613)	1.04 (1.00-1.08) (0.0602)	1.04 (1.00-1.08) (0.0805)	1.04 (1.00-1.08) (0.0728)
Socioeconomic status								
1 (poorest)	3107/249692	1.24 (1.20-1.29)	0.84 (0.80-0.88)	0.78 (0.74-0.81)	0.86 (0.81-0.91)	0.95 (0.89-1.01)	0.96 (0.90-1.02)	0.96 (0.90-1.02)
2	3349/249775	1.34 (1.30-1.39)	0.91 (0.87-0.95)	0.86 (0.82-0.90)	0.92 (0.88-0.97)	0.99 (0.94-1.04)	0.99 (0.94-1.05)	1.00 (0.94-1.05)
3	3471/252903	1.37 (1.33-1.42)	0.93 (0.89-0.97)	0.88 (0.84-0.93)	0.93 (0.89-0.98)	0.98 (0.93-1.03)	0.98 (0.93-1.03)	0.98 (0.93-1.03)
4	3587/254568	1.41 (1.36-1.46)	0.95 (0.91-1.00)	0.92 (0.88-0.97)	0.95 (0.91-1.00)	0.98 (0.93-1.03)	0.98 (0.94-1.03)	0.98 (0.94-1.03)
5 (richest)	3718/251859	1.48 (1.43-1.52)	ref (<0.0001)	ref	ref (<0.0001)	ref (0.4947)	ref (0.5364)	ref (0.5398)
Maternal occupation								
Gov/Private/Other	1001/65037	1.54 (1.45-1.64)	1.08(1.01-1.16)	1.14 (1.06-1.21)	1.09 (1.02-1.17)	1.09 (1.02-1.16)	1.09 (1.02-1.17)	1.09 (1.02-1.17)
Self-employed	6937/487861	1.42 (1.39-1.46)	ref	ref	ref	ref	ref	ref
Farming	4754/370833	1.28 (1.25-1.32)	0.90 (0.87-0.94)	0.86 (0.83-0.89)	0.93 (0.89-0.97)	0.95 (0.91-0.99)	0.95 (0.91-0.99)	0.95 (0.91-0.99)
Does not work	4540/335066	1.35 (1.32-1.39)	0.95 (0.92-0.99) (<0.0001)	0.93 (0.90-0.97)	0.94 (0.91-0.98) (<0.0001)	0.99 (0.95-1.03) (0.0039)	0.99 (0.95-1.03) (0.0033)	0.99 (0.95-1.03) (0.0031)

Continued……

Table 5.6 continued

	Vaccinations / Person days of follow-up	Vaccination Rate / 100 days of follow-up	Unadjusted Rate Ratios RR (95%CI) (p-value)	Rate Ratios adjusted for age-band* aRR (95%CI) (p-value)	Rate Ratios adjusted for distal determinants aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants and birth weight aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants and birth weight and illness aRR (95%CI) (p-value)
Maternal education								
None	5021/395418	1.27 (1.24-1.31)	0.88 (0.85-0.91)	0.83 (0.80-0.86)	0.89 (0.85-0.93)	0.88 (0.84-0.92)	0.88 (0.84-0.92)	0.88 (0.84-0.92)
Primary school	3115/233158	1.34 (1.29-1.38)	0.93 (0.89-0.96)	0.89 (0.86-0.93)	0.93 (0.89-0.97)	0.93 (0.89-0.97)	0.93 (0.89-0.97)	0.93 (0.89-0.97)
Secondary / tertiary	9096/630221	1.44 (1.41-1.47)	ref	ref	ref	ref	ref	ref
			(<0.0001)		(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
Season vaccine due								
Wet	10996/798445	1.38 (1.35-1.40)	ref	ref	ref	ref	ref	ref
Dry	6236/460352	1.35 (1.32-1.39)	0.98 (0.95-1.01)	0.98 (0.95-1.01)	0.98 (0.95-1.01)	0.98 (0.95-1.01)	0.98 (0.95-1.01)	0.98 (0.95-1.01)
			(0.2971)		(0.1892)	(0.2185)	(0.1961)	(0.1817)
Sex								
Male	8711/639311	1.36 (1.33-1.39)	ref	ref	ref	ref	ref	ref
Female	8521/619486	1.38 (1.35-1.41)	1.01 (0.98-1.04)	1.01 (0.98-1.04)	1.01 (0.98-1.04)	1.01 (0.98-1.05)	1.02 (0.99-1.05)	1.02 (0.99-1.05)
			(0.5352)		(0.3939)	(0.3503)	(0.2095)	(0.2206)
Intermediate Determinants								
Maternal age (years)								
15 – 19	1864/145995	1.28 (1.22-1.34)	0.90 (0.86-0.95)	0.86 (0.82-0.91)		0.83 (0.77-0.88)	0.84 (0.78-0.89)	0.84 (0.78-0.89)
20 – 24	4388/321687	1.36 (1.32-1.41)	0.97 (0.93-1.01)	0.95 (0.91-0.99)		0.93 (0.89-0.97)	0.93 (0.89-0.98)	0.93 (0.89-0.98)
25 – 29	4752/336462	1.41 (1.37-1.45)	ref	ref		ref	ref	ref
30 – 34	3507/253443	1.38 (1.34-1.43)	0.98 (0.94-1.02)	0.97 (0.93-1.02)		1.02 (0.98-1.07)	1.03 (0.98-1.07)	1.03 (0.98-1.07)
35 years and over	2721/201210	1.35 (1.30-1.40)	0.96 (0.91-1.00)	0.94 (0.89-0.98)		1.02 (0.96-1.07)	1.02 (0.97-1.08)	1.02 (0.97-1.08)
			(0.0053)			(<0.0001)	(<0.0001)	(<0.0001)
Number of living children in family								
0-1	5061/365082	1.39 (1.35-1.43)	1.00 (0.96-1.03)	1.00 (0.96-1.03)		1.04 (0.99-1.08)	1.05 (1.00-1.09)	1.05 (1.00-1.10)
2-3	6996/502347	1.39 (1.36-1.43)	ref	ref		ref	ref	ref
4 or more	5175/391368	1.32 (1.29-1.36)	0.95 (0.92-0.98)	0.93 (0.90-0.96)		0.96 (0.92-1.00)	0.95 (0.91-1.00)	0.95 (0.91-1.00)
			(0.0103)			(0.0249)	(0.0068)	(0.0066)

Continued……

Table 5.6 continued

	Vaccinations / Person days of follow-up	Vaccination Rate / 100 days of follow-up	Unadjusted Rate Ratios RR (95%CI) (p-value)	Rate Ratios adjusted for age-band* aRR (95%CI) (p-value)	Rate Ratios adjusted for distal determinants aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants and birth weight aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants and birth weight and illness aRR (95%CI) (p-value)
Maternal illness								
No	16379/1197898	1.37 (1.35-1.39)	ref	ref		ref	ref	ref
Yes	853/60899	1.40 (1.31-1.50)	1.02 (0.96-1.10) (0.4939)	1.04 (0.97-1.12)		1.05 (0.98-1.12) (0.1900)	1.05 (0.98-1.13) (0.1454)	1.05 (0.98-1.13) (0.1319)
Distance from health facility								
<1.00km	10715/754658	1.42 (1.39-1.45)	ref	ref		ref	ref	ref
1.00-4.99km	3960/292241	1.36 (1.31-1.40)	0.95 (0.92-0.99)	0.93 (0.89-0.96)		0.94 (0.90-0.97)	0.94 (0.90-0.97)	0.94 (0.90-0.97)
>=5.00km	2557/211898	1.21 (1.16-1.25)	0.85 (0.81-0.89) (<0.0001)	0.79 (0.76-0.83)		0.86 (0.82-0.90) (<0.0001)	0.86 (0.82-0.90) (<0.0001)	0.86 (0.82-0.91) (<0.0001)
Place of birth								
Facility	13485/959719	1.41 (1.38-1.43)	ref	ref		ref	ref	ref
Non-facility	3747/299078	1.25 (1.21-1.30)	0.89 (0.86-0.92) (<0.0001)	0.85 (0.82-0.88)		0.94 (0.90-0.98) (0.0048)	0.94 (0.91-0.98) (0.0072)	0.94 (0.91-0.98) (0.0065)
Multiple birth								
No	16648/1213539	1.37 (1.35-1.39)	ref	ref		ref	ref	ref
Yes	584/45258	1.29 (1.19-1.40)	0.94 (0.87-1.02) (0.1420)	0.92 (0.85-1.00)		0.94 (0.86-1.02) (0.1256)	1.04 (0.95-1.13) (0.4219)	1.04 (0.95-1.13) (0.4172)
Proximal Variables								
Birth weight								
>=2.5kg	14759/1065163	1.39 (1.36-1.41)	ref	ref			ref	ref
2.00-2.49kg	2185/166348	1.31 (1.26-1.37)	0.95 (0.91-0.99)	0.92 (0.88-0.96)			0.93 (0.89-0.97)	0.93 (0.89-0.97)
1.50-1.99kg	243/22400	1.08 (0.96-1.23)	0.78 (0.69-0.89)	0.72 (0.64-0.82)			0.71 (0.62-0.81)	0.71 (0.63-0.81)
<1.50kg	45/4886	0.92 (0.69-1.23)	0.66 (0.50-0.89) (<0.0001)	0.58 (0.43-0.77)			0.58 (0.43-0.77) (<0.0001)	0.58 (0.43-0.78) (<0.0001)
Mediating Variables								
Infant illness								
No	2040/155146	1.31 (1.26-1.37)	ref	ref				ref
Yes	15192/1103651	1.38 (1.35-1.40)	0.96 (0.91-1.00) (0.0507)	0.94 (0.90-0.99)				0.95 (0.91-1.00) (0.0949)

** all p-values<0.0001*

Table 5.7: Determinants of DTP3 vaccination between 0 and 18 weeks

	Vaccinations / Person days of follow-up	Vaccination Rate / 100 days of follow-up	Unadjusted Rate Ratios	Rate Ratios adjusted for age-band*	Rate Ratios adjusted for distal determinants	Rate Ratios adjusted for distal and intermediate determinants	Rate Ratios adjusted for distal and intermediate determinants and birth weight	Rate Ratios adjusted for distal and intermediate determinants and birth weight and illness
			RR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)
Infant age-band (in days)								
29.5-60.0	72/1991481	0.00 (0.00-0.00)	0.00 (0.00-0.00)	_	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
>90.0	9252/648138	1.43 (1.40-1.46)	Ref (<0.0001)	_	ref (<0.0001)	ref	ref	ref
Distal Determinants								
Religion of head of household								
Christian	6914/1839099	0.38 (0.37-0.38)	ref	ref	ref	ref	ref	ref
Muslim	1826/633930	0.29 (0.28-0.30)	0.77 (0.73-0.81)	0.74 (0.71-0.78)	0.81 (0.76-0.85)	0.81 (0.76-0.86)	0.81 (0.76-0.86)	0.81 (0.77-0.86)
None/Traditional/Other	584/166590	0.35 (0.32-0.38)	0.93 (0.86-1.01) (<0.0001)	0.93 (0.85-1.01)	0.99 (0.91-1.08) (<0.0001)	1.01 (0.93-1.11) (<0.0001)	1.01 (0.93-1.10) (<0.0001)	1.01 (0.93-1.10) (<0.0001)
Ethnicity of household								
Akan	4742/1236481	0.38 (0.37-0.39)	ref	ref	ref	ref	ref	ref
Other	4582/1403138	0.33 (0.32-0.34)	0.85 (0.82-0.89) (<0.0001)	0.84 (0.81-0.88)	1.03 (0.98-1.08) (0.2939)	1.03 (0.97-1.08) (0.3212)	1.03 (0.97-1.08) (0.3537)	1.03 (0.97-1.08) (0.3484)
Socioeconomic status								
1 (poorest)	1643/513227	0.32 (0.31-0.34)	0.87 (0.81-0.93)	0.85 (0.80-0.91)	0.97 (0.90-1.05)	1.12 (1.03-1.22)	1.13 (1.04-1.23)	1.13 (1.04-1.23)
2	1823/518697	0.35 (0.34-0.37)	0.95 (0.89-1.02)	0.95 (0.89-1.01)	1.03 (0.96-1.10)	1.15 (1.07-1.23)	1.15 (1.07-1.24)	1.15 (1.07-1.24)
3	1935/527519	0.37 (0.35-0.38)	1.00 (0.94-1.06)	0.99 (0.93-1.06)	1.05 (0.98-1.12)	1.13 (1.05-1.20)	1.13 (1.06-1.21)	1.13 (1.06-1.21)
4	1925/538101	0.36 (0.34-0.37)	0.97 (0.91-1.03)	0.97 (0.91-1.03)	1.01 (0.95-1.08)	1.05 (0.99-1.12)	1.05 (0.99-1.12)	1.05 (0.99-1.12)
5 (richest)	1998/542075	0.37 (0.35-0.39)	ref (<0.0001)	ref	ref (0.2542)	Ref (0.0016)	ref (0.0011)	Ref (0.0010)
Maternal occupation								
Gov/Private/Other	581/141110	0.41 (0.38-0.45)	1.16 (1.06-1.27)	1.19 (1.09-1.30)	1.12 (1.02-1.22)	1.11 (1.01-1.21)	1.11 (1.01-1.21)	1.11 (1.01-1.21)
Self-employed	3680/1036780	0.35 (0.34-0.37)	ref	ref	ref	ref	ref	ref
Farming	2618/764688	0.34 (0.33-0.36)	0.96 (0.92-1.01)	0.96 (0.91-1.01)	1.04 (0.98-1.10)	1.07 (1.00-1.13)	1.07 (1.00-1.13)	1.07 (1.00-1.13)
Does not work	2445/697041	0.35 (0.34-0.36)	0.99 (0.94-1.04) (0.0013)	0.99 (0.94-1.04)	0.98 (0.93-1.03) (0.0203)	1.05 (0.99-1.11) (0.0372)	1.05 (0.99-1.11) (0.0388)	1.05 (0.99-1.11) (0.0394)

Continued……

Table 5.7 continued

	Vaccinations / Person days of follow-up	Vaccination Rate / 100 days of follow-up	Unadjusted Rate Ratios RR (95%CI) (p-value)	Rate Ratios adjusted for age-band* aRR (95%CI) (p-value)	Rate Ratios adjusted for distal determinants aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants and birth weight aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants and birth weight and illness aRR (95%CI) (p-value)
Maternal education								
None	2473/819833	0.30 (0.29-0.31)	0.77 (0.73-0.81)	0.74 (0.71-0.78)	0.77 (0.73-0.82)	0.77 (0.72-0.81)	0.77 (0.72-0.81)	0.77 (0.72-0.81)
Primary school	1614/486863	0.33 (0.32-0.35)	0.84 (0.80-0.89)	0.82 (0.78-0.87)	0.84 (0.79-0.89)	0.85 (0.80-0.90)	0.85 (0.80-0.90)	0.85 (0.80-0.90)
Secondary / tertiary	5237/1332923	0.39 (0.38-0.40)	ref	ref	ref	ref	ref	ref
			(<0.0001)		(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
Season vaccine due								
Wet	4476/1240162	0.36 (0.35-0.37)	ref	ref	ref	ref	ref	ref
Dry	4848/1399457	0.35 (0.34-0.36)	0.96 (0.92-1.00)	0.97 (0.93-1.01)	0.96 (0.92-1.00)	0.96 (0.92-1.00)	0.96 (0.92-1.00)	0.96 (0.92-1.00)
			(0.0480)		(0.0692)	(0.0580)	(0.0522)	(0.0511)
Sex								
Male	4679/1340011	0.35 (0.34-0.36)	ref	ref	ref	ref	ref	ref
Female	4645/12990608	0.36 (0.35-0.37)	1.02 (0.98-1.07)	1.03 (0.99-1.07)	1.03 (0.99-1.07)	1.03 (0.99-1.07)	1.03 (0.99-1.08)	1.03 (0.99-1.08)
			(0.2602)		(0.1865)	(0.1668)	(0.1145)	(0.1165)
Intermediate Determinants								
Maternal age (years)								
15 – 19	947/299973	0.32 (0.30-0.34)	0.87 (0.80-0.93)	0.85 (0.79-0.92)		0.76 (0.70-0.84)	0.77 (0.70-0.84)	0.77 (0.70-0.84)
20 – 24	2373/670758	0.35 (0.34-0.37)	0.97 (0.92-1.03)	0.97 (0.92-1.03)		0.93 (0.88-0.99)	0.93 (0.88-0.99)	0.93 (0.88-0.99)
25 – 29	2593/711054	0.36 (0.35-0.38)	ref	ref		ref	ref	ref
30 – 34	1931/534971	0.36 (0.35-0.38)	0.99 (0.93-1.05)	0.99 (0.93-1.05)		1.06 (0.99-1.13)	1.06 (0.99-1.13)	1.06 (0.99-1.13)
35 years and over	1480/422863	0.35 (0.33-0.37)	0.96 (0.90-1.02)	0.95 (0.89-1.01)		1.06 (0.98-1.14)	1.06 (0.99-1.14)	1.06 (0.99-1.14)
			(0.0030)			(<0.0001)	(<0.0001)	(<0.0001)
Number of living children in family								
0-1	2760/764387	0.36 (0.35-0.37)	1.00 (0.95-1.05)	1.00 (0.96-1.05)		1.06 (1.00-1.13)	1.07 (1.01-1.13)	1.07 (1.01-1.13)
2-3	3818/1055899	0.36 (0.35-0.37)	ref	ref		ref	ref	ref
4 or more	2746/819333	0.34 (0.32-0.35)	0.93 (0.88-0.97)	0.92 (0.87-0.96)		0.92 (0.87-0.98)	0.92 (0.86-0.97)	0.92 (0.86-0.97)
			(0.0039)			(0.0018)	(0.0007)	(0.0004)
Maternal illness								
No	8869/2510288	0.35 (0.35-0.36)	ref	ref		ref	ref	ref
Yes	455/129331	0.35 (0.32-0.39)	1.00 (0.91-1.09)	1.00 (0.91-1.10)		1.01 (0.92-1.11)	1.02 (0.92-1.12)	1.02 (0.93-1.12)
			(0.9296)			(0.8125)	(0.7333)	(0.7234)

Continued……

Table 5.7 continued

	Vaccinations / Person days of follow-up	Vaccination Rate / 100 days of follow-up	Unadjusted Rate Ratios RR (95%CI) (p-value)	Rate Ratios adjusted for age-band* aRR (95%CI) (p-value)	Rate Ratios adjusted for distal determinants aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants and birth weight aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants and birth weight and illness aRR (95%CI) (p-value)
Distance from health facility								
<1.00km	5957/1597445	0.37 (0.36-0.38)	ref	ref		ref	ref	ref
1.00-4.99km	2110/608508	0.35 (0.33-0.36)	0.93 (0.88-0.98)	0.92 (0.87-0.96)		0.90 (0.86-0.95)	0.90 (0.86-0.95)	0.90 (0.86-0.95)
>=5.00km	1257/433666	0.29 (0.27-0.31)	0.78 (0.73-0.83) (<0.0001)	0.76 (0.71-0.80)		0.79 (0.74-0.84) (<0.0001)	0.79 (0.74-0.84) (<0.0001)	0.79 (0.74-0.84) (<0.0001)
Place of birth								
Facility	7394/2025562	0.37 (0.36-0.37)	ref	ref		ref	ref	ref
Non-facility	1930/614057	0.31 (0.30-0.33)	0.86 (0.82-0.91) (<0.0001)	0.85 (0.81-0.89)		0.94 (0.88-0.99) (0.0213)	0.94 (0.89-0.99) (0.0282)	0.94 (0.89-0.99) (0.0281)
Multiple birth								
No	8997/2546020	0.35 (0.35-0.36)	ref	ref		ref	ref	ref
Yes	327/93599	0.35 (0.31-0.39)	0.99 (0.89-1.10) (0.8390)	0.98 (0.88-1.10)		1.01 (0.90-1.13) (0.8669)	1.10 (0.98-1.24) (0.1243)	1.10 (0.98-1.24) (0.1225)
Proximal Variables								
Birth weight								
>=2.5kg	8007/2240325	0.36 (0.35-0.37)	ref	ref			ref	ref
2.00-2.49kg	1168/344907	0.34 (0.32-0.36)	0.95 (0.89-1.01)	0.94 (0.88-0.99)			0.93 (0.88-0.99)	0.93 (0.88-0.99)
1.50-1.99kg	132/45006	0.29 (0.25-0.35)	0.82 (0.69-0.97)	0.81 (0.68-0.96)			0.78 (0.66-0.93)	0.78 (0.66-0.93)
<1.50kg	17/9381	0.18 (0.11-0.29)	0.51 (0.32-0.82) (0.0005)	0.48 (0.30-0.78)			0.46 (0.29-0.75) (<0.0001)	0.46 (0.29-0.75) (<0.0001)
Mediating Variables								
Infant illness								
No	7935/2232383	0.36 (0.35-0.36)	ref	ref				ref
Yes	1389/407236	0.34 (0.32-0.36)	0.96 (0.91-1.02) (0.1540)	0.96 (0.91-1.01)				1.02 (0.96-1.08) (0.2632)

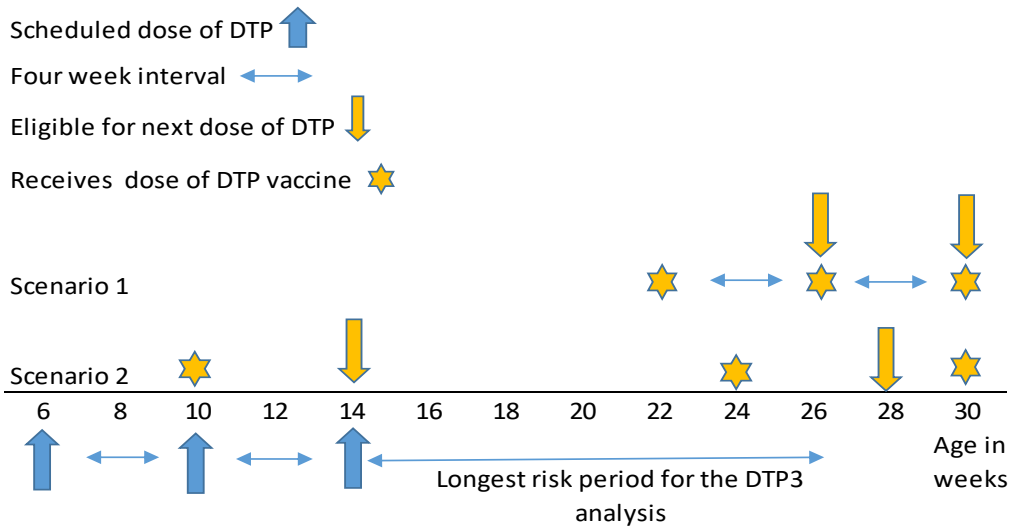
** all p-values<0.0001*

5.7.4. How does controlling for delayed administration of DTP1 affect estimates of the effect of determinants of DTP3 vaccination rate?

As discussed in **Chapter 3**, in Ghana, DTP is recommended to be given in a three-dose schedule, with a minimum four-week interval between doses. Consequently, delayed administration of DTP1 will necessitate delayed administration of the subsequent doses of DTP, in order to comply with the recommended staging of the vaccine. For this reason, analyses of vaccination timing which measure vaccination within fixed risk (time) periods may include infants who are not in fact late for vaccination, as they are not yet eligible for vaccination due to the delayed receipt of earlier doses.

In my main analyses of DTP3 vaccination I analysed the vaccination rate from the scheduled due date of 14 weeks of age, up to 26 weeks of age (12 weeks after the vaccine due date). **Figure 5.2** illustrates two theoretical scenarios in which infants who were included in this analysis could have been misclassified as being vaccinated late, when they were in fact not yet eligible for DTP3 vaccination.

Figure 5.2: Delayed receipt of DTP1 and DTP2, and the subsequent impact on timing of DTP3 vaccination.



In both scenarios the initiation of DTP vaccination for the infant is late. In the first scenario the infant subsequently complies with the schedule and receives each subsequent dose four weeks after the previous dose. In the second scenario the infant is also delayed in receiving the later doses of DTP. In both scenarios the infant does not become eligible for DTP3 until after the end of the risk period for the DTP3 analysis. In both scenarios the infant will have been classified as not vaccinated at the end of the risk period, when in fact they

were not yet eligible for vaccination with DTP3. In the first scenario delayed receipt of DTP1 drives delayed receipt of DTP3. In the second scenario delayed receipt of DTP3 is driven not only by delayed receipt of DTP1, but also by factors that caused additional delayed administration of DTP2 and DTP3. Delayed receipt of DTP1 may influence the determinants of DTP3 vaccination.

Few studies of vaccination timing have actually accounted for delayed receipt of earlier doses in the analysis[4-7]. In an analysis of the determinants of time to DTP2 and DTP3 vaccination using Cox regression undertaken in Tanzania, infants only contributed time to the analysis from the date of the previous dose in the series[4]. In an American study, Luman et al[5], when calculating days under-vaccinated due to delayed vaccination in the first two years of life, undertook a primary analysis based on the routine schedule, and a secondary analysis whereby they applied a catch-up schedule, which incorporated a minimum interval between doses, to account for the timing of earlier doses in the series. In this American study, accounting for the timing of earlier doses caused a decline in the mean number of days under-vaccinated from 172 days to 163 days; there was little difference in the proportion of children under-vaccinated for more than six months (37% declined to 36%)[5]. Another American study[6] included timely vaccination with each of DTP1, 2 and 3 (defined as receiving these vaccines on time, or late (>1 month after the due date)) as explanatory variables when modelling the determinants of DTP4 by two years of age, and found that timeliness of DTP2 and DTP3 were the biggest predictors of DTP4 vaccination. Similarly, Dayan et al[7], in an analysis of delayed vaccination in Argentina, reported that late receipt of DTP1 was a strong predictor of delayed receipt of DTP4 (not having received DTP4 at 19 months of age).

In my primary analyses of DTP3 vaccination, I did not account for delayed receipt of DTP1 and DTP2. Among the 22192 infants included in this analysis, 2566 (12%) were unvaccinated at 26 weeks of age (the latest defined end of the risk period for DTP3). Of these 2566, 1388 (54%) were vaccinated with DTP1 more than four weeks after the DTP1 due date, and 2254 (88%) were vaccinated with DTP2 more than four weeks after the DTP2 due date. Infants who were delayed in receipt of DTP3 were also delayed in receiving DTP2 and DTP1.

In order to explore how delayed receipt of earlier scheduled doses may have affected the effect estimates of the determinants of DTP3 vaccination, I undertook an additional sensitivity analysis of the DTP3 vaccination rate within 12 weeks of receipt of DTP1. Overall,

accounting for delayed receipt of DTP1 made little difference to the results of the analysis of determinants of DTP3 vaccination rate (**Table 5.8** - DTP3 vaccination within 12 weeks of DTP1 vaccination); although there were a small number of exceptions as explained below.

As discussed in **Section 5.7.3**, at 12 weeks after the vaccine due date, compared to infants from the richest quintile of SES, those from lower quintiles had moderately higher vaccination rate ratios (**Appendix 5.1, Table A5.5**). When late vaccination with DTP1 was accounted for, the association between SES and vaccination was similar to that observed for DTP1, whereby a weak association was observed in the distal model that was no longer observed following adjustment for intermediate variables.

As discussed in the paper, accounting for delayed DTP1 vaccination made little difference to the estimated association between birth weight and DTP3 vaccination, for VLBW infants; although the observed size of the association for MLBW infants declined such that the vaccination rate for MLBW infants was similar to NLBW infants. This could suggest that the lower DTP3 vaccination rate for MLBW infants may be due to their lower DTP1 vaccination rate whereas VLBW infants have lower DTP3 vaccination rates, irrespective of when they received DTP1. This is interesting as it supports the hypothesis that the effect of fragility associated with LBW declines with infant age; here, having accounted for delayed DTP1, we can see a persisting effect for only the most fragile, smallest infants.

Finally, a moderate association between ethnicity and DTP3 vaccination rate was observed within 12 weeks of DTP1 vaccination, which was not observed for DTP3 vaccination within 12 weeks of the due date. Having accounted for delayed DTP1, infants of non-Akan ethnicity were observed to have moderately higher vaccination rates than infants of Akan ethnicity (aOR=1.10; 95%CI:1.05-1.14). The implications of this finding for the vaccination programme are unclear, although the maximum 14% difference (from the upper 95% confidence interval) in vaccination rates between Akan and non-Akan may not be of substantive public health significance.

Overall it appears that accounting for delayed receipt of DTP1 makes little difference to the factors associated with DTP3 vaccination in the three months after the vaccine due date. This is important as it suggests that preventing delayed DTP1 vaccination will not automatically eliminate delayed DTP3 vaccination. Strategies to improve the timeliness of vaccination will also need to target vaccines due later in the schedule.

Table 5.8: Sensitivity analysis 3, Determinants of DTP3 vaccination within 12 weeks of vaccination with DTP1

	Vaccinations / Person days of follow-up	Vaccination Rate / 100 days of follow-up	Unadjusted Rate Ratios	Rate Ratios adjusted for age-band*	Rate Ratios adjusted for distal determinants	Rate Ratios adjusted for distal and intermediate determinants	Rate Ratios adjusted for distal and intermediate determinants and birth weight	Rate Ratios adjusted for distal and intermediate determinants and birth weight and illness
			RR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)
Infant age-band (in days)	0/96426	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
<29.5	207/100911	0.21 (0.18-0.24)	ref	ref	ref	ref	ref	ref
29.5-60.0	10055/200276	5.02 (4.92-5.12)	24.47 (21.33-28.09)	24.42 (21.28-28.02)	24.42 (21.28-28.02)	24.42 (21.28-28.02)	24.42 (21.28-28.02)	24.41 (21.27-28.01)
60.1-90.0	2726/48422	5.63 (5.42-5.85)	27.44 (23.83-31.61)	28.42 (24.67-32.74)	28.78 (24.98-32.74)	28.84 (25.04-33.22)	28.84 (25.04-33.22)	28.84 (25.04-33.22)
>90.0			(<0.0001)		(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
Distal Determinants								
Religion of head of household								
Christian	9591/297907	3.22 (3.16-3.28)	ref	ref	ref	ref	ref	ref
Muslim	2589/116463	2.22 (2.14-2.31)	0.69 (0.66-0.72)	0.83 (0.79-0.87)	0.83 (0.79-0.87)	0.84 (0.80-0.88)	0.84 (0.80-0.88)	0.84 (0.80-0.88)
None/Traditional/Other	808/31665	2.55 (2.38-2.73)	0.79 (0.74-0.85)	0.90 (0.83-0.96)	0.90 (0.83-0.96)	0.91 (0.85-0.98)	0.91 (0.85-0.98)	0.91 (0.85-0.98)
			(<0.0001)		(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
Ethnicity of household								
Akan	6552/201540	3.25 (3.17-3.33)	ref	ref	ref	ref	ref	ref
Other	6436/244495	2.63 (2.57-2.70)	0.81 (0.78-0.84)	1.09 (1.04-1.14)	1.09 (1.04-1.14)	1.09 (1.05-1.14)	1.09 (1.05-1.14)	1.10 (1.05-1.14)
			(<0.0001)		(0.0001)	(0.0001)	(0.0001)	(0.0001)
Socioeconomic status								
1 (poorest)	2355/95845	2.46 (2.36-2.56)	0.75 (0.71-0.79)	0.86 (0.81-0.92)	0.86 (0.81-0.92)	0.94 (0.88-1.01)	0.94 (0.88-1.01)	0.94 (0.88-1.01)
2	2591/89903	2.88 (2.77-3.00)	0.87 (0.83-0.92)	0.92 (0.86-0.97)	0.92 (0.86-0.97)	0.97 (0.92-1.04)	0.97 (0.92-1.04)	0.98 (0.92-1.04)
3	2728/93108	2.93 (2.82-3.04)	0.89 (0.84-0.94)	0.91 (0.86-0.96)	0.91 (0.86-0.96)	0.95 (0.89-1.00)	0.95 (0.89-1.00)	0.95 (0.90-1.00)
4	2653/86402	3.07 (2.96-3.19)	0.93 (0.88-0.98)	0.94 (0.89-0.99)	0.94 (0.89-0.99)	0.97 (0.92-1.02)	0.97 (0.92-1.02)	0.97 (0.92-1.02)
5 (richest)	2661/80777	3.29 (3.17-3.42)	ref	ref	ref	ref	ref	ref
			(<0.0001)		(0.2541)	(0.2953)	(0.2953)	(0.3126)
Maternal occupation								
Gov/Private/Other	740/22834	3.24 (3.02-3.48)	1.05 (0.98-1.14)	1.06 (0.98-1.14)	1.06 (0.98-1.14)	1.04 (0.96-1.13)	1.04 (0.96-1.13)	1.04 (0.96-1.13)
Self-employed	5045/164173	3.07 (2.99-3.16)	ref	ref	ref	ref	ref	ref
Farming	3770/131945	2.86 (2.77-2.95)	0.93 (0.89-0.97)	0.99 (0.94-1.04)	0.99 (0.94-1.04)	1.01 (0.96-1.06)	1.01 (0.96-1.06)	1.01 (0.96-1.06)
Does not work	3433/127083	2.70 (2.61-2.79)	0.88 (0.84-0.92)	0.93 (0.89-0.97)	0.93 (0.89-0.97)	0.97 (0.92-1.01)	0.97 (0.92-1.01)	0.97 (0.92-1.01)
			(<0.0001)		(0.1945)	(0.2128)	(0.2128)	(0.2192)

Continues….

Table 5.9 continued

	Vaccinations / Person days of follow-up	Vaccination Rate / 100 days of follow-up	Unadjusted Rate Ratios	Rate Ratios adjusted for distal determinants	Rate Ratios adjusted for distal and intermediate determinants	Rate Ratios adjusted for distal and intermediate determinants and birth weight	Rate Ratios adjusted for distal and intermediate determinants and birth weight and illness
			RR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)
Maternal education							
None	3599/148371	2.43 (2.35-2.51)	0.73 (0.71-0.76)	0.84 (0.80-0.89)	0.84 (0.80-0.89)	0.84 (0.80-0.89)	0.84 (0.80-0.89)
Primary school	2246/81442	2.76 (2.65-2.87)	0.83 (0.80-0.88)	0.90 (0.86-0.95)	0.92 (0.87-0.96)	0.92 (0.87-0.96)	0.92 (0.87-0.96)
Secondary / tertiary	7143/216222	3.30 (3.23-3.38)	ref	ref	ref	ref	ref
			(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
Season vaccine due							
Wet	6185/203450	3.04 (2.97-3.12)	ref	ref	ref	ref	ref
Dry	6803/242585	2.80 (2.74-2.87)	0.92 (0.89-0.95)	1.00 (0.96-1.03)	1.00 (0.96-1.03)	1.00 (0.96-1.03)	1.00 (0.96-1.03)
			(<0.0001)	(0.8354)	(0.7997)	(0.7997)	(0.7924)
Sex							
Male	6511/228848	2.85 (2.78-2.92)	ref	ref	ref	ref	ref
Female	6477/217187	2.98 (2.91-3.06)	1.05 (1.01-1.08)	1.04 (1.00-1.07)	1.04 (1.00-1.08)	1.04 (1.00-1.08)	1.04 (1.00-1.08)
			(0.0073)	(0.0484)	(0.0294)	(0.0294)	(0.0292)
Intermediate determinants							
Maternal age (years)							
15 – 19	1414/56814	2.49 (2.36-2.62)	0.83 (0.78-0.88)		0.82 (0.76-0.88)	0.82 (0.76-0.89)	0.82 (0.76-0.89)
20 – 24	3283/116673	2.81 (2.72-2.91)	0.94 (0.89-0.98)		0.95 (0.90-1.00)	0.95 (0.90-1.00)	0.95 (0.90-1.00)
25 – 29	3565/118844	3.00 (2.90-3.10)	ref		ref	ref	ref
30 – 34	2655/85740	3.10 (2.98-3.22)	1.03 (0.98-1.09)		1.08 (1.03-1.14)	1.08 (1.03-1.14)	1.08 (1.03-1.14)
35 years and over	2071/67964	3.05 (2.92-3.18)	1.02 (0.96-1.07)		1.09 (1.02-1.16)	1.09 (1.02-1.16)	1.09 (1.02-1.16)
			(<0.0001)		(<0.0001)	(<0.0001)	(<0.0001)
Number of living children in family							
0-1	3851/131361	2.93 (2.84-3.03)	0.97 (0.93-1.01)		1.08 (1.02-1.13)	1.08 (1.03-1.14)	1.08 (1.03-1.14)
2-3	5281/174233	3.03 (2.95-3.11)	ref		ref	ref	ref
4 or more	3856/140441	2.75 (2.66-2.83)	0.91 (0.87-0.94)		0.90 (0.86-0.95)	0.90 (0.85-0.95)	0.90 (0.85-0.95)
			(<0.0001)		(<0.0001)	(<0.0001)	(<0.0001)
Maternal illness							
No	12352/425249	2.90 (2.85-2.96)	ref		ref	ref	ref
Yes	636/20786	3.06 (2.83-3.31)	1.05 (0.97-1.14)		1.06 (0.98-1.15)	1.07 (0.98-1.16)	1.07 (0.99-1.16)
			(0.2043)		(0.1490)	(0.1185)	(0.1121)

Continued….

Table 5.9 continued

	Vaccinations / Person days of follow-up	Vaccination Rate / 100 days of follow-up	Unadjusted Rate Ratios	Rate Ratios adjusted for age-band*	Rate Ratios adjusted for distal determinants	Rate Ratios adjusted for distal and intermediate determinants	Rate Ratios adjusted for distal and intermediate determinants and birth weight	Rate Ratios adjusted for distal and intermediate determinants and birth weight and illness
			RR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)
Distance from health facility	8056/270041	2.98 (2.92-3.05)	ref			ref	ref	ref
<1.00km	3089/99637	3.10 (2.99-3.21)	1.04 (1.00-1.08)			1.00 (0.96-1.04)	1.00 (0.96-1.04)	1.00 (0.96-1.04)
1.00-4.99km	1843/76357	2.41 (2.31-2.53)	0.81 (0.77-0.85)			0.92 (0.87-0.98)	0.92 (0.87-0.98)	0.93 (0.88-0.98)
>=5.00km			(<0.0001)			(0.0176)	(0.0191)	(0.0204)
Place of birth								
Facility	10170/331942	3.06 (3.00-3.12)	ref			ref	ref	ref
Non-facility	2818/114093	2.47 (2.38-2.56)	0.81 (0.77-0.84)			0.93 (0.89-0.97)	0.93 (0.89-0.98)	0.93 (0.89-0.98)
			(<0.0001)			(0.0022)	(0.0032)	(0.0032)
Multiple birth								
No	12544/429864	2.92 (2.87-2.97)	ref			ref	ref	ref
Yes	444/16171	2.75 (2.50-3.01)	0.94 (0.86-1.03)			0.95 (0.87-1.05)	1.00 (0.91-1.11)	1.00 (0.91-1.11)
			(0.2028)			(0.3379)	(0.09652)	(0.9593)
Proximal Variables								
Birth weight								
>=2.5kg	11090/375642	2.95 (2.90-3.01)	ref				ref	ref
2.00-2.49kg	1664/60515	2.75 (2.62-2.89)	0.93 (0.88-0.98)				0.93 (0.88-0.98)	0.93 (0.88-0.98)
1.50-1.99kg	202/7548	2.68 (2.33-3.07)	0.91 (0.79-1.04)				0.98 (0.85-1.13)	0.98 (0.85-1.12)
<1.50kg	32/2330	1.37 (0.97-1.94)	0.47 (0.33-0.66)				0.65 (0.46-0.92)	0.65 (0.46-0.93)
			(<0.0001)				(0.0065)	(0.0069)
Mediating Variables								
Infant illness								
No	11075/371786	2.98 (2.92-3.03)	ref					ref
Yes	1913/74249	2.58 (2.46-2.69)	0.86 (0.82-0.91)					1.02 (0.98-1.08)
			(<0.0001)					(0.6120)

** all p-values<0.0001*

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APPENDIX 5.1

Table A5.1. Comparison of estimated effect of determinants of DTP1 and DTP3 vaccination, analysed by Poisson and Cox regression*

	DTP1 between 0 and 18 weeks		DTP3 between 0 and 26 weeks	
	Rate Ratios aRR (95%CI)	Hazard Ratios aHR (95%CI)	Rate Ratios aRR (95%CI)	Hazard Ratios aHR (95%CI)
Distal Determinants				
Religion				
Christian	ref	ref	ref	ref
Muslim	0.92 (0.89-0.95)	0.82 (0.89-0.95)	0.82 (0.79-0.85)	0.82 (0.78-0.85)
None/Traditional/Other	0.96 (0.90-1.01)	0.95 (0.90-1.01)	0.94 (0.88-1.00)	0.94 (0.88-1.00)
Ethnicity of household				
	ref	ref	ref	ref
Akan	1.03 (0.99-1.06)	1.04 (1.01-1.08)	0.97 (0.94-1.01)	0.98 (0.94-1.01)
Other				
Socioeconomic status				
1 (poorest)	0.94 (0.89-0.99)	0.93 (0.88-0.98)	1.09 (1.03-1.16)	1.09 (1.03-1.16)
2	0.99 (0.95-1.04)	0.98 (0.93-1.02)	1.14 (1.08-1.20)	1.14 (1.09-1.21)
3	0.99 (0.95-1.04)	0.97 (0.93-1.02)	1.11 (1.05-1.16)	1.11 (1.06-1.17)
4	0.99 (0.95-1.03)	0.98 (0.94-1.02)	1.06 (1.01-1.11)	1.06 (1.01-1.11)
5 (richest)	ref	ref	ref	ref
Maternal occupation				
Gov/Private/Other	1.08 (1.01-1.15)	1.10 (1.03-1.17)	1.07 (1.01-1.15)	1.08 (1.01-1.16)
Self-employed	ref	ref	ref	ref
Farming	0.97 (0.93-1.01)	0.95 (0.92-0.99)	1.09 (1.04-1.13)	1.09 (1.04-1.13)
Does not work	0.99 (0.96-1.03)	0.99 (0.95-1.03)	1.02 (0.98-1.06)	1.02 (0.98-1.07)
Maternal education				
None	0.88 (0.84-0.91)	0.86 (0.83-0.90)	0.78 (0.75-0.82)	0.77 (0.74-0.81)
Primary school	0.93 (0.89-0.96)	0.92 (0.88-0.95)	0.83 (0.80-0.87)	0.83 (0.79-0.86)
Secondary / tertiary	ref	ref	ref	ref
Season vaccine due				
Wet	ref	ref	ref	ref
Dry	1.00 (0.97-1.02)	1.00 (0.97-1.02)	0.96 (0.92-0.98)	0.95 (0.92-0.98)
Sex				
Male	ref	ref	ref	ref
Female	1.02 (1.00-1.05)	1.03 (1.00-1.05)	1.04 (1.01-1.07)	1.04 (1.01-1.07)
Intermediate determinants				
Maternal age (years)				
15 – 19	0.84 (0.79-0.89)	0.82 (0.77-0.87)	0.80 (0.75-0.85)	0.79 (0.74-0.84)
20 – 24	0.93 (0.89-0.97)	0.92 (0.89-0.96)	0.91 (0.87-0.95)	0.91 (0.87-0.95)
25 – 29	ref	ref	ref	ref
30 – 34	1.02 (0.98-1.07)	1.03 (0.99-1.07)	1.07 (1.02-1.12)	1.07 (1.03-1.12)
35 years and over	1.02 (0.97-1.07)	1.02 (0.97-1.07)	1.06 (1.01-1.12)	1.07 (1.01-1.12)
Number of living children in family				
0-1	1.05 (1.01-1.09)	1.06 (1.02-1.11)	1.07 (1.03-1.12)	1.08 (1.03-1.13)
2-3	ref	ref	ref	ref
4 or more	0.95 (0.91-0.99)	0.95 (0.91-0.99)	0.88 (0.85-0.92)	0.88 (0.85-0.92)

Continued….

Table A5.1 continued

	DTP1 between 0 and 18 weeks		DTP3 between 0 and 26 weeks	
	Rate Ratios aRR (95%CI)	Hazard Ratios aHR (95%CI)	Rate Ratios aRR (95%CI)	Hazard Ratios aHR (95%CI)
Maternal illness				
No	ref	ref	ref	ref
Yes	1.03 (0.97-1.10)	1.04 (0.98-1.11)	0.98 (0.92-1.05)	0.98 (0.92-1.05)
Distance from health facility				
<1.00km	ref	ref	ref	ref
1.00-4.99km	0.96 (0.93-0.99)	0.95 (0.92-0.98)	0.98 (0.95-1.02)	0.98 (0.94-1.01)
>=5.00km	0.87 (0.83-0.91)	0.86 (0.82-0.90)	0.81 (0.77-0.85)	0.81 (0.77-0.85)
Place of birth				
Facility	ref	ref	ref	ref
Non-facility	0.94 (0.91-0.98)	0.93 (0.90-0.97)	0.95 (0.91-0.99)	0.95 (0.91-0.98)
Multiple birth				
No	ref	ref	ref	ref
Yes	1.08 (1.00-1.17)	1.09 (1.00-1.17)	1.07 (0.98-1.16)	1.07 (0.99-1.17)
Distal Determinants				
Birth weight				
>=2.5kg	ref	ref	ref	ref
2.00-2.49kg	0.92 (0.89-0.96)	0.91 (0.88-0.95)	0.95 (0.91-1.00)	0.95 (0.91-0.99)
1.50-1.99kg	0.77 (0.69-0.85)	0.75 (0.67-0.84)	0.82 (0.73-0.92)	0.82 (0.73-0.92)
<1.50kg	0.64 (0.51-0.80)	0.61 (0.49-0.78)	0.60 (0.46-0.79)	0.59 (0.45-0.78)
Mediating Variables				
Infant illness				
No	ref	ref	ref	ref
Yes	0.94 (0.90-0.98)	0.94 (0.91-0.98)	1.03 (0.99-1.07)	0.97 (0.94-1.02)

** Effect estimates adjusted for infant age-band, for distal, intermediate and proximal variables, and for the mediating effects of infant illness. Poisson model adjusted for infant age.*

Table A5.2: Sensitivity analysis 1: Determinants of DTP1 vaccination between 0 and 18 weeks of age (omitting those infants reported not vaccinated but whose card was never seen)

	Unadjusted Rate Ratios	Rate Ratios adjusted for age-band*	Rate Ratios adjusted for distal determinants	Rate Ratios adjusted for distal and intermediate determinants	Rate Ratios adjusted for distal and intermediate determinants and birth weight	Rate Ratios adjusted for distal and intermediate determinants and birth weight & illness
	RR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)
Infant age-band (in days)						
<29.5	0.01 (0.01-0.01)	_	0.01 (0.01-0.01)	0.01 (0.01-0.01)	0.01 (0.01-0.01)	0.01 (0.01-0.01)
29.5-60.0	*ref*	_	*ref*	*ref*	*ref*	*ref*
60.1-90.0	2.25 (2.18-2.31)	_	2.29 (2.22-2.36)	2.31 (2.24-2.38)	2.32 (2.25-2.38)	2.32 (2.25-2.39)
>90.0	1.57 (1.48-1.67)	_	1.64 (1.55-1.74)	1.67 (1.57-1.77)	1.68 (1.58-1.78)	1.68 (1.58-1.78)
	(<0.0001)		(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
Distal Determinants						
Religion of head of household						
Christian	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
Muslim	0.95 (0.92-0.98)	0.88 (0.86-0.91)	0.92 (0.89-0.95)	0.93 (0.89-0.96)	0.92 (0.89-0.96)	0.93 (0.89-0.96)
None/Traditional/Other	0.94 (0.89-0.99)	0.87 (0.82-0.92)	0.94 (0.89-1.00)	0.95 (0.90-1.01)	0.95 (0.90-1.01)	0.95 (0.90-1.01)
	(0.0007)		(<0.0001)	(0.0001)	(0.0001)	(0.0001)
Ethnicity of household						
Akan	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
Other	0.95 (0.93-0.98)	0.89 (0.87-0.92)	1.02 (0.98-1.05)	1.02 (0.99-1.06)	1.02 (0.98-1.05)	1.02 (0.98-1.05)
	(0.0006)		(0.3032)	(0.2601)	(0.3357)	(0.2996)
Socioeconomic status						
1 (poorest)	0.90 (0.86-0.93)	0.77 (0.74-0.81)	0.86 (0.82-0.90)	0.95 (0.90-1.00)	0.96 (0.91-1.01)	0.96 (0.91-1.01)
2	0.94 (0.90-0.98)	0.87 (0.83-0.91)	0.93 (0.89-0.98)	1.00 (0.95-1.05)	1.00 (0.96-1.05)	1.01 (0.96-1.05)
3	0.96 (0.92-1.00)	0.91 (0.87-0.94)	0.95 (0.91-0.99)	0.99 (0.95-1.04)	1.00 (0.96-1.04)	1.00 (0.96-1.04)
4	0.97 (0.93-1.01)	0.93 (0.90-0.97)	0.96 (0.92-1.01)	0.99 (0.95-1.03)	0.99 (0.95-1.03)	0.99 (0.95-1.03)
5 (richest)	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
	(<0.0001)		(<0.0001)	(0.2343)	(0.2535)	(0.2478)
Maternal occupation						
Gov/Private/Other	1.05 (0.99-1.11)	1.12 (1.06-1.19)	1.08 (1.01-1.15)	1.08 (1.01-1.15)	0.08 (0.01-1.15)	1.08 (1.01-1.15)
Self-employed	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
Farming	0.94 (0.91-0.97)	0.87 (0.84-0.90)	0.95 (0.91-0.99)	0.97 (0.93-1.00)	0.96 (0.93-1.00)	0.96 (0.93-1.00)
Does not work	0.97 (0.94-1.01)	0.93 (0.90-0.97)	0.95 (0.92-0.98)	0.99 (0.96-1.03)	0.99 (0.96-1.03)	0.99 (0.96-1.03)
	(0.0004)		(0.0001)	(0.0223)	(0.0182)	(0.0179)

Continued…..

Table A5.2 continued

	Unadjusted Rate Ratios RR (95%CI) (p-value)	Rate Ratios adjusted for age-band* aRR (95%CI) (p-value)	Rate Ratios adjusted for distal determinants aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants and birth weight aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants and birth weight & illness aRR (95%CI) (p-value)
Maternal education						
None	0.92 (0.89-0.95)	0.82 (0.80-0.85)	0.89 (0.86-0.93)	0.88 (0.85-0.92)	0.88 (0.85-0.92)	0.88 (0.85-0.92)
Primary school	0.95 (0.92-0.99)	0.88 (0.85-0.91)	0.92 (0.88-0.95)	0.92 (0.89-0.96)	0.93 (0.89-0.96)	0.93 (0.89-0.96)
Secondary / tertiary	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
	(<0.0001)		(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
Season vaccine due						
Wet	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
Dry	1.00 (0.97-1.03)	0.99 (0.97-1.02)	0.99 (0.97-1.02)	0.99 (0.97-1.02)	0.99 (0.97-1.02)	0.99 (0.97-1.02)
	(0.9539)		(0.6101)	(0.6972)	(0.6439)	(0.6030)
Sex						
Male	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
Female	1.01 (0.98-1.03)	1.02 (0.99-1.04)	1.01 (0.99-1.04)	1.01 (0.99-1.04)	1.02 (0.99-1.05)	1.02 (0.99-1.05)
	(0.6079)		(0.3246)	(0.2974)	(0.1590)	(0.1714)
Intermediate Determinants						
Maternal age (years)						
15 – 19	0.94 (0.90-0.98)	0.87 (0.83-0.91)		0.83 (0.78-0.88)	0.84 (0.79-0.89)	0.84 (0.79-0.89)
20 – 24	0.98 (0.94-1.01)	0.95 (0.91-0.98)		0.93 (0.89-0.96)	0.93 (0.89-0.97)	0.93 (0.89-0.97)
25 – 29	*ref*	*ref*		*ref*	*ref*	*ref*
30 – 34	0.99 (0.95-1.03)	0.97 (0.94-1.01)		1.03 (0.98-1.07)	1.03 (0.99-1.07)	1.03 (0.99-1.07)
35 years and over	0.97 (0.93-1.02)	0.94 (0.90-0.98)		1.02 (0.97-1.07)	1.02 (0.97-1.07)	1.02 (0.97-1.07)
	(0.1103)			(<0.0001)	(<0.0001)	(<0.0001)
Number of living children in family	1.00 (0.97-1.03)	0.99 (0.96-1.03)		1.04 (1.00-1.08)	1.05 (1.01-1.09)	1.05 (1.01-1.09)
0-1	*ref*	*ref*		*ref*	*ref*	*ref*
2-3	0.97 (0.94-1.00)	0.93 (0.90-0.96)		0.95 (0.92-0.99)	0.95 (0.91-0.99)	0.95 (0.91-0.99)
4 or more	(0.1759)			(0.0049)	(0.0009)	(0.0008)
Maternal illness						
No	*ref*	*ref*		*ref*	*ref*	*ref*
Yes	1.01 (0.95-1.07)	1.02 (0.96-1.08)		1.02 (0.96-1.09)	1.03 (0.96-1.09)	1.03 (0.97-1.09)
				(0.5027)	(0.4304)	(0.4033)

Continued…

Table A5.2 continued

	Unadjusted Rate Ratios	Rate Ratios adjusted for age-band*	Rate Ratios adjusted for distal determinants	Rate Ratios adjusted for distal and intermediate determinants	Rate Ratios adjusted for distal and intermediate determinants and birth weight	Rate Ratios adjusted for distal and intermediate determinants and birth weight & illness
	RR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)
Distance from health facility						
<1.00km	*ref*	*ref*		*ref*	*ref*	*ref*
1.00-4.99km	0.98 (0.95-1.01)	0.95 (0.92-0.98)		0.96 (0.93-0.99)	0.96 (0.93-0.99)	0.96 (0.93-0.99)
>=5.00km	0.91 (0.87-0.94) (<0.0001)	0.79 (0.77-0.83)		0.87 (0.83-0.91) (<0.0001)	0.87 (0.83-0.91) (<0.0001)	0.87 (0.84-0.91) (<0.0001)
Place of birth						
Facility	*ref*	*ref*		*ref*	*ref*	*ref*
Non-facility	0.93 (0.90-0.96) (<0.0001)	0.84 (0.82-0.87)		0.94 (0.91-0.97) (0.0009)	0.94 (0.91-0.98) (0.0014)	0.94 (0.91-0.98) (0.0012)
Multiple birth						
No	*ref*	*ref*		*ref*	*ref*	*ref*
Yes	0.99 (0.92-1.06) (0.7293)	0.96 (0.89-1.03)		0.98 (0.91-1.05) (0.5892)	1.08 (1.00-1.17) (0.0492)	1.08 (1.00-1.17) (0.0473)
Proximal Variables						
Birth weight						
>=2.5kg	*ref*	*ref*			*ref*	*ref*
2.00-2.49kg	0.97 (0.93-1.00)	0.92 (0.88-0.96)			0.92 (0.89-0.96)	0.92 (0.89-0.96)
1.50-1.99kg	0.90 (0.82-1.00)	0.79 (0.71-0.88)			0.76 (0.69-0.85)	0.76 (0.69-0.85)
<1.50kg	0.81 (0.65-1.02) (0.0215)	0.64 (0.51-0.80)			0.63 (0.50-0.79) (<0.0001)	0.63 (0.50-0.79) (<0.0001)
Mediating Variables						
Infant illness						
No	*ref*	*ref*				*ref*
Yes	0.97 (0.93-1.01) (0.1219)	0.93 (0.90-0.97)				0.95 (0.91-0.99) (0.0039)

** all p-values<0.0001*

Table A5.3: Sensitivity analysis 2: determinants of delayed DTP3 vaccination in rural Ghana and between 0 and 26 weeks of age (omitting those infants reported not vaccinated but whose card was never seen).

	Unadjusted Rate Ratios	Rate Ratios adjusted for age-band*	Rate Ratios adjusted for distal determinants	Rate Ratios adjusted for distal and intermediate determinants	Rate Ratios adjusted for distal and intermediate determinants and birth weight	Rate Ratios adjusted for distal and intermediate determinants and birth weight & illness
	RR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)
Infant age-band (in days)						
<29.5	0.00 (0.00-0.00)	_	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
29.5-60.0	ref	_	ref	ref	ref	ref
60.1-90.0	1.92 (1.86-1.98)	_	1.96 (1.90-2.02)	1.97 (1.91-2.04)	1.98 (1.91-2.04)	1.98 (1.91-2.04)
>90.0	1.78 (1.71-1.85)	_	1.87 (1.79-1.94)	1.90 (1.82-1.97)	1.9 (1.82-1.98)	1.90 (1.82-1.98)
	(<0.0001)		(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
Distal Determinants						
Religion of head of household						
Christian	ref	ref	ref	ref	ref	ref
Muslim	0.84 (0.81-0.87)	0.73 (0.70-0.76)	0.81 (0.78-0.85)	0.82 (0.79-0.86)	0.82 (0.79-0.86)	0.82 (0.79-0.86)
None/Traditional/Other	0.91 (0.86-0.97)	0.85 (0.80-0.90)	0.92 (0.86-0.98)	0.94 (0.88-1.00)	0.93 (0.88-0.99)	0.93 (0.88-0.99)
	(<0.0001)		(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
Ethnicity of household						
Akan	ref	ref	ref	ref	ref	ref
Other	0.88 (0.86-0.91)	0.80 (0.77-0.82)	0.97 (0.93-1.01)	0.97 (0.94-1.01)	0.97 (0.93-1.01)	0.97 (0.93-1.01)
	(<0.0001)		(0.1107)	(0.1280)	(0.1122)	(0.1172)
Socioeconomic status						
1 (poorest)	0.90 (0.86-0.94)	0.83 (0.79-0.87)	0.96 (0.90-1.01)	1.10 (1.04-1.17)	1.1 (1.04-1.17)	1.10 (1.04-1.17)
2	0.98 (0.93-1.02)	0.96 (0.92-1.00)	1.04 (0.99-1.09)	1.15 (1.09-1.21)	1.15 (1.09-1.21)	1.15 (1.09-1.21)
3	0.99 (0.94-1.03)	0.99 (0.94-1.03)	1.04 (0.99-1.09)	1.11 (1.05-1.16)	1.11 (1.06-1.16)	1.11 (1.06-1.16)
4	0.99 (0.94-1.03)	0.98 (0.93-1.02)	1.02 (0.98-1.07)	1.06 (1.01-1.11)	1.06 (1.01-1.11)	1.06 (1.01-1.11)
5 (richest)	ref	ref	ref	ref	ref	ref
	(<0.0001)		(0.0031)	(<0.0001)	(<0.0001)	(<0.0001)
Maternal occupation						
Gov/Private/Other	1.07 (1.00-1.14)	1.16 (1.09-1.24)	1.09 (1.02-1.16)	1.08 (1.01-1.15)	1.08 (1.01-1.15)	1.08 (1.01-1.15)
Self-employed	ref	ref	ref	ref	ref	ref
Farming	0.98 (0.94-1.01)	0.96 (0.93-0.99)	1.05 (1.01-1.10)	0.90 (0.04-0.13)	1.09 (1.04-1.13)	1.09 (1.04-1.13)
Does not work	0.98 (0.94-1.01)	0.97 (0.94-1.01)	0.97 (0.93-1.01)	1.02 (0.98-1.07)	1.02 (0.98-1.07)	1.02 (0.98-1.07)
	(0.0428)		(0.0001)	(0.0005)	(0.0006)	(0.0006)

Continued….

Table A5.3 continued

	Unadjusted Rate Ratios	Rate Ratios adjusted for age-band*	Rate Ratios adjusted for distal determinants	Rate Ratios adjusted for distal and intermediate determinants	Rate Ratios adjusted for distal and intermediate determinants and birth weight	Rate Ratios adjusted for distal and intermediate determinants and birth weight & illness
	RR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)
Maternal education						
None	0.85 (0.82-0.87)	0.73 (0.70-0.75)	0.79 (0.76-0.82)	0.90 (0.75-0.82)	0.78 (0.75-0.82)	0.78 (0.75-0.82)
Primary school	0.89 (0.86-0.93)	0.79 (0.76-0.82)	0.82 (0.79-0.86)	0.90 (0.80-0.87)	0.83 (0.80-0.87)	0.83 (0.80-0.87)
Secondary / tertiary	ref	ref	ref	ref	ref	ref
	(<0.0001)		(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
Season vaccine due						
Wet	ref	ref	ref	ref	ref	ref
Dry	0.97 (0.94-1.00)	0.96 (0.93-0.99)	0.95 (0.93-0.98)	0.90 (0.92-0.98)	0.95 (0.92-0.98)	0.95 (0.92-0.98)
	(0.0550)		(0.0011)	(0.0005)	(0.0004)	(0.0003)
Sex						
Male	ref	ref	ref	ref	ref	ref
Female	1.02 (0.99-1.05)	1.03 (1.00-1.06)	1.03 (1.00-1.06)	1.03 (1.00-1.06)	1.03 (1.00-1.06)	1.03 (1.00-1.06)
	(0.2878)		(0.0586)	(0.0464)	(0.0290)	(0.0304)
Intermediate Determinants						
Maternal age (years)						
15 – 19	0.93 (0.88-0.98)	0.88 (0.84-0.93)		0.79 (0.74-0.84)	0.8 (0.75-0.85)	0.80 (0.75-0.85)
20 – 24	0.96 (0.93-1.00)	0.94 (0.91-0.98)		0.90 (0.86-0.94)	0.9 (0.87-0.94)	0.90 (0.87-0.94)
25 – 29	ref	ref		ref	ref	ref
30 – 34	1.00 (0.95-1.04)	0.98 (0.94-1.03)		1.07 (1.02-1.12)	1.07 (1.02-1.12)	1.07 (1.02-1.12)
35 years and over	0.97 (0.93-1.02)	0.94 (0.89-0.98)		1.06 (1.01-1.12)	1.06 (1.01-1.12)	1.06 (1.01-1.12)
	(0.0316)			(<0.0001)	(<0.0001)	(<0.0001)
Number of living children in family	0.99 (0.96-1.03)	1.00 (0.96-1.03)		1.06 (1.02-1.11)	1.07 (1.03-1.12)	1.07 (1.03-1.12)
0-1	ref	ref		ref	ref	ref
2-3	0.95 (0.92-0.98)	0.89 (0.86-0.93)		0.90 (0.85-0.92)	0.88 (0.84-0.92)	0.88 (0.84-0.92)
4 or more	(0.0063)			(<0.0001)	(<0.0001)	(<0.0001)
Maternal illness						
No	ref	ref		ref	ref	ref
Yes	0.98 (0.92-1.05)	0.97 (0.91-1.04)		0.98 (0.91-1.05)	0.98 (0.92-1.05)	0.98 (0.92-1.05)
	(0.5948)			(0.5023)	(0.5535)	(0.5719)

Continued….

Table A5.3 continued

	Unadjusted Rate Ratios	Rate Ratios adjusted for age-band*	Rate Ratios adjusted for distal determinants	Rate Ratios adjusted for distal and intermediate determinants	Rate Ratios adjusted for distal and intermediate determinants and birth weight	Rate Ratios adjusted for distal and intermediate determinants and birth weight & illness
	RR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)
Distance from health facility						
<1.00km	ref	ref		ref	ref	ref
1.00-4.99km	1.01 (0.98-1.05)	1.01 (0.97-1.04)		0.98 (0.94-1.01)	0.98 (0.94-1.01)	0.98 (0.95-1.02)
>=5.00km	0.88 (0.84-0.91) (<0.0001)	0.77 (0.74-0.81)		0.90 (0.77-0.85) (<0.0001)	0.81 (0.78-0.85) (<0.0001)	0.81 (0.78-0.85) (<0.0001)
Place of birth						
Facility	ref	ref		ref	ref	ref
Non-facility	0.92 (0.89-0.95) (<0.0001)	0.86 (0.83-0.89)		0.95 (0.91-0.99) (0.0092)	0.95 (0.91-0.99) (0.0121)	0.95 (0.91-0.99) (0.0120)
Multiple birth						
No	ref	ref		ref	ref	ref
Yes	0.98 (0.91-1.06) (0.5997)	0.95 (0.88-1.03)		0.99 (0.92-1.08) (0.8962)	1.07 (0.98-1.16) (0.1247)	1.07 (0.98-1.17) (0.1197)
Proximal Variables						
Birth weight						
>=2.5kg	ref	ref			ref	ref
2.00-2.49kg	0.97 (0.93-1.02)	0.95 (0.91-0.99)			0.95 (0.91-1.00)	0.95 (0.91-1.00)
1.50-1.99kg	0.92 (0.82-1.03)	0.86 (0.77-0.96)			0.82 (0.73-0.93)	0.82 (0.73-0.92)
<1.50kg	0.73 (0.56-0.97) (0.0336)	0.62 (0.47-0.82)			0.6 (0.45-0.79) (<0.0001)	0.60 (0.45-0.79) (<0.0001)
Mediating Variables						
Infant illness						
No	ref	ref				ref
Yes	0.97 (0.93-1.01) (0.1191)	0.95 (0.91-0.99)				1.02 (0.98-1.07) (0.1151)

** All p-values<0.0001*

Table A5.4 Determinants of DTP1 vaccination between 0 and 14 weeks

	Vaccinations / Person days of follow-up	Vaccination Rate / 100 days of follow-up	Unadjusted Rate Ratios RR (95%CI) (p-value)	Rate Ratios adjusted for age-band* aRR (95%CI) (p-value)	Rate Ratios adjusted for distal determinants aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants and birth weight aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants and birth weight and illness aRR (95%CI) (p-value)
Infant age-band (in days)								
<29.5	130/670092	0.02 (0.02-0.02)	0.01 (0.01-0.01)	_	0.01 (0.01-0.01)	0.01 (0.01-0.01)	0.01 (0.01-0.01)	0.01 (0.01-0.01)
29.5-60.0	13098/524434	2.50 (2.46-2.54)	ref	_	ref	ref	ref	ref
>90.0	7657/140213	5.46 (5.34-5.58)	2.19 (2.13-2.25) (<0.0001)		2.23 (2.17-2.30) (<0.0001)	2.25 (2.19-2.32) (<0.0001)	2.26 (2.20-2.33) (<0.0001)	2.26 (2.20-2.33) (<0.0001)
Distal Determinants								
Religion of head of household								
Christian	14757/923943	1.60 (1.57-1.62)	ref	ref	ref	ref	ref	ref
Muslim	4834/324362	1.49 (1.45-1.53)	0.93 (0.90-0.96)	0.88 (0.85-0.90)	0.91 (0.88-0.95)	0.92 (0.88-0.95)	0.92 (0.88-0.95)	0.92 (0.88-0.95)
None/Traditional/Other	1294/86434	1.50 (1.42-1.58)	0.94 (0.89-0.99) (<0.0001)	0.88 (0.83-0.93)	0.96 (0.90-1.01) (<0.0001)	0.97 (0.91-1.02) (<0.0001)	0.97 (0.91-1.02) (<0.0001)	0.97 (0.91-1.02) (<0.0001)
Ethnicity of household								
Akan	9959/617164	1.61 (1.58-1.65)	ref	ref	ref	ref	ref	ref
Other	10926/717575	1.52 (1.49-1.55)	0.94 (0.92-0.97) (<0.0001)	0.89 (0.87-0.92)	1.03 (0.99-1.06) (0.1641)	1.03 (0.99-1.07) (0.1162)	1.03 (0.99-1.06) (0.1532)	1.03 (0.99-1.06) (0.1332)
Socioeconomic status								
1 (poorest)	3915/269995	1.45 (1.41-1.50)	0.88 (0.84-0.92)	0.76 (0.73-0.80)	0.85 (0.81-0.90)	0.94 (0.89-0.99)	0.95 (0.89-1.00)	0.95 (0.89-1.00)
2	4089/265346	1.54 (1.49-1.59)	0.93 (0.89-0.97)	0.86 (0.82-0.90)	0.93 (0.88-0.97)	0.99 (0.95-1.04)	1.00 (0.95-1.05)	1.00 (0.95-1.05)
3	4223/267384	1.58 (1.53-1.63)	0.95 (0.92-1.00)	0.90 (0.86-0.94)	0.94 (0.90-0.99)	0.99 (0.95-1.03)	0.99 (0.95-1.04)	0.99 (0.95-1.04)
4	4294/268139	1.60 (1.55-1.65)	0.97 (0.93-1.01)	0.93 (0.89-0.97)	0.96 (0.92-1.00)	0.99 (0.94-1.03)	0.99 (0.95-1.03)	0.99 (0.95-1.03)
5 (richest)	4364/263875	1.65 (1.61-1.70)	ref (<0.0001)	ref	ref (<0.0001)	ref (0.1604)	ref (0.1886)	Ref (0.1862)
Maternal occupation								
Gov/Private/Other	1149/67828	1.69 (1.60-1.79)	1.05 (0.99-1.12)	1.12 (1.05-1.19)	1.08 (1.01-1.14)	1.08 (1.01-1.14)	1.08 (1.01-1.15)	1.08 (1.01-1.15)
Self-employed	8275/513801	1.61 (1.58-1.65)	ref	ref	ref	ref	ref	ref
Farming	5946/397315	1.50 (1.46-1.54)	0.93 (0.90-0.96)	0.86 (0.83-0.89)	0.94 (0.90-0.98)	0.96 (0.92-0.99)	0.95 (0.92-0.99)	0.95 (0.92-0.99)
Does not work	5515/355795	1.55 (1.51-1.59)	0.96 (0.93-1.00) (<0.0001)	0.93 (0.89-0.96)	0.94 (0.91-0.97) (<0.0001)	0.99 (0.95-1.02) (0.0088)	0.99 (0.95-1.03) (<0.0001)	0.99 (0.95-1.02) (0.0068)

Continued….

Table A5.4 continued

	Vaccinations / Person days of follow-up	Vaccination Rate / 100 days of follow-up	Unadjusted Rate Ratios	Rate Ratios adjusted for age-band*	Rate Ratios adjusted for distal determinants	Rate Ratios adjusted for distal and intermediate determinants	Rate Ratios adjusted for distal and intermediate determinants and birth weight	Rate Ratios adjusted for distal and intermediate determinants and birth weight and illness
			RR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)
Maternal education								
None	6283/425582	1.48 (1.44-1.51)	0.90 (0.88-0.93)	0.81 (0.79-0.84)	0.88 (0.85-0.92)	0.88 (0.84-0.91)	0.88 (0.84-0.91)	0.88 (0.84-0.91)
Primary school	3813/248478	1.53 (1.49-1.58)	0.94 (0.91-0.98)	0.88 (0.84-0.91)	0.92 (0.88-0.95)	0.92 (0.88-0.96)	0.92 (0.89-0.96)	0.92 (0.89-0.96)
Secondary / tertiary	10789/660679	1.63 (1.60-1.66)	ref	ref	ref	ref	ref	ref
			(<0.0001)		(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
Season vaccine due								
Wet	13239/846115	1.56(1.54-1.59)	ref	ref	ref	ref	ref	ref
Dry	7646/488624	1.56 (1.53-1.60)	1.00 (0.97-1.03)	0.99 (0.97-1.02)	0.99 (0.97-1.02)	0.99 (0.97-1.02)	0.99 (0.97-1.02)	0.99 (0.97-1.02)
			(0.9957)		(0.6477	(0.7241)	(0.6733)	(0.6309)
Sex								
Male	10574/678792	1.56 (1.53-1.59)	ref	ref	ref	ref	ref	ref
Female	10311/655947	1.57 (1.54-1.60)	1.01 (0.98-1.04)	1.02 (0.99-1.05)	1.02 (0.99-1.04)	1.02 (0.99-1.05)	1.02 (1.00-1.05)	1.02 (1.00-1.05)
			(0.5133)		(0.2102)	(0.1996)	(0.0955)	(0.1080)
Intermediate determinants								
Maternal age (years)								
15 – 19	2334/156279	1.49 (1.43-1.56)	0.93 (0.89-0.98)	0.87 (0.83-0.91)		0.84 (0.79-0.89)	0.85 (0.80-0.90)	0.85 (0.80-0.90)
20 – 24	5307/341400	1.55 (1.51-1.60)	0.97 (0.94-1.01)	0.95 (0.91-0.98)		0.93 (0.89-0.97)	0.93 (0.90-0.97)	0.93 (0.90-0.97)
25 – 29	5672/355058	1.60 (1.56-1.64)	ref	ref		ref	ref	ref
30 – 34	4241/268454	1.58 (1.53-1.63)	0.99 (0.95-1.03)	0.97 (0.94-1.01)		1.03 (0.98-1.07)	1.03 (0.99-1.07)	1.03 (0.99-1.07)
35 years and over	3331/213548	1.56 (1.51-1.61)	0.98 (0.94-1.02)	0.95 (0.91-0.99)		1.02 (0.97-1.07)	1.03 (0.98-1.08)	1.02 (0.98-1.08)
			(0.0840)			(<0.0001)	(<0.0001)	(<0.0001)
Number of living children in family								
0-1	6084/386564	1.57 (1.53-1.61)	0.99 (0.96-1.03)	0.99 (0.96-1.02)		1.03 (0.99-1.07)	1.04 (1.00-1.08)	1.04 (1.00-1.08)
2-3	8401/530639	1.58 (1.55-1.62)	ref	ref		ref	ref	ref
4 or more	6400/417536	1.53 (1.50-1.57)	0.97 (0.94-1.00)	0.93 (0.90-0.96)		0.96 (0.92-1.00)	0.95 (0.91-0.99)	0.95 (0.91-0.99)
			(0.1290)			(0.0233)	(0.0055)	(0.0052)
Maternal illness								
No	19861/1270022	1.56 (1.54-1.59)	ref	ref		ref	ref	ref
Yes	1024/64717	1.58 (1.49-1.68)	1.01 (0.95-1.08)	1.02 (0.96-1.09)		1.02 (0.96-1.09)	1.03 (0.97-1.10)	1.03 (0.97-1.10)
			(0.7150)			(0.4595)	(0.3811)	(0.3535)

Continued….

Table A5.4 continued

	Vaccinations / Person days of follow-up	Vaccination Rate / 100 days of follow-up	Unadjusted Rate Ratios	Rate Ratios adjusted for age-band*	Rate Ratios adjusted for distal determinants	Rate Ratios adjusted for distal and intermediate determinants	Rate Ratios adjusted for distal and intermediate determinants and birth weight	Rate Ratios adjusted for distal and intermediate determinants and birth weight and illness
			RR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)
Distance from health facility								
<1.00km	12750/795837	1.60 (1.57-1.63)	ref	ref		ref	ref	ref
1.00-4.99km	4843/308623	1.57 (1.53-1.61)	0.98 (0.95-1.01)	0.95 (0.92-0.98)		0.96 (0.93-0.99)	0.96 (0.93-0.99)	0.96 (0.93-1.00)
>=5.00km	3292/230279	1.43 (1.38-1.48)	0.89 (0.86-0.93) (<0.0001)	0.79 (0.76-0.82)		0.87 (0.83-0.90) (<0.0001)	0.87 (0.83-0.91) (<0.0001)	0.87 (0.83-0.91) (<0.0001)
Place of birth								
Facility	16169/1012397	1.60 (1.57-1.62)	ref	ref		ref	ref	ref
Non-facility	4716/322342	1.46 (1.42-1.51)	0.92 (0.89-0.95) (<0.0001)	0.84 (0.81-0.87)		0.94 (0.90-0.97) (0.0006)	0.94 (0.91-0.98) (0.0010)	0.94 (0.90-0.97) (0.0009)
Multiple birth								
No	20147/1286294	1.57 (1.54-1.59)	ref	ref		ref	ref	ref
Yes	738/48445	1.52 (1.42-1.64)	0.97 (0.90-1.05) (0.4567)	0.94 (0.87-1.01)		0.96 (0.89-1.03) (0.2355)	1.06 (0.98-1.14) (0.1838)	1.06 (0.98-1.14) (0.1773)
Proximal Variables								
Birth weight								
>=2.5kg	17789/1126945	1.58 (1.56-1.60)	ref	ref			ref	ref
2.00-2.49kg	2680/177815	1.51 (1.45-1.57)	0.95 (0.92-0.99)	0.91 (0.88-0.95)			0.92 (0.88-0.96)	0.92 (0.88-0.96)
1.50-1.99kg	347/24482	1.42 (1.28-1.57)	0.90 (0.81-1.00)	0.79 (0.71-0.88)			0.77 (0.69-0.86)	0.77 (0.69-0.86)
<1.50kg	69/5497	1.26 (0.99-1.59)	0.80 (0.63-1.01) (0.0064)	0.63 (0.50-0.80)			0.62 (0.49-0.79) (<0.0001)	0.63 (0.49-0.80) (<0.0001)
Mediating Variables								
Infant illness								
No	2508/165931	1.51 (1.45-1.57)	ref	ref				ref
Yes	18377/1168808	1.57 (1.55-1.60)	0.96 (0.92-1.00) (0.0626)	0.93 (0.89-0.97)				0.94 (0.90-0.98) (0.0076)

** All p-values<0.0001*

Table A5.5: Determinants of DTP1 vaccination between 0 and 18 weeks.

	Vaccinations / Person days of follow-up	Vaccination Rate / 100 days of follow-up	Unadjusted Rate Ratios	Rate Ratios adjusted for age-band*	Rate Ratios adjusted for distal determinants	Rate Ratios adjusted for distal and intermediate determinants	Rate Ratios adjusted for distal and intermediate determinants and birth weight	Rate Ratios adjusted for distal and intermediate determinants and birth weight & illness
			RR (95%CI)	aRR (95%CI)	aRR (95%CI)	aRR (95%CI)	aRR (95%CI)	aRR (95%CI)
Infant age-band (in days)								
<29.5	130/670092	0.02 (0.02-0.02)	0.01 (0.01-0.01)	_	0.01 (0.01-0.01)	0.01 (0.01-0.01)	0.01 (0.01-0.01)	0.01 (0.01-0.01)
29.5-60.0	13098/524434	2.50 (2.46-2.54)	ref	_	ref	ref	ref	ref
60.1-90.0	7176/129054	5.56 (5.43-5.69)	2.23 (2.16-2.29)	_	2.27 (2.21-2.34)	2.29 (2.23-2.36)	2.30 (2.23-2.37)	2.30 (2.24-2.37)
>90.0	1272/34095	3.73 (3.53-3.94)	1.49 (1.41-1.58)	_	1.56 (1.48-1.66)	1.59 (1.50-1.68)	1.60 (1.50-1.69)	1.60 (1.51-1.69)
			(<0.0001)		(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
Distal Determinants								
Religion of head of household								
Christian	15229/936775	1.63 (1.60-1.65)	ref	ref	ref	ref	ref	ref
Muslim	5100/332362	1.53 (1.49-1.58)	0.94 (0.91-0.97)	0.88 (0.85-0.91)	0.91 (0.88-0.95)	0.92 (0.89-0.95)	0.92 (0.89-0.95)	0.92 (0.89-0.95)
None / Traditional / Other	1347/88538	1.52 (1.44-1.60)	0.94 (0.89-0.99)	0.87 (0.82-0.92)	0.95 (0.89-1.00)	0.96 (0.90-1.01)	0.95 (0.90-1.01)	0.96 (0.90-1.01)
			(0.0003)		(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
Ethnicity of household	10241/624937	1.64 (1.61-1.67)	ref	ref	ref	ref	ref	ref
Akan	11435/732738	1.56 (1.53-1.59)	0.95 (0.93-0.98)	0.89 (0.87-0.92)	1.03 (0.99-1.06)	1.03 (0.99-1.07)	1.03 (0.99-1.06)	1.03 (0.99-1.06)
Other			(0.0003)		(0.1215)	(0.1011)	(0.1387)	(0.1196)
Socioeconomic status								
1 (poorest)	4135/277198	1.49 (1.45-1.54)	0.89 (0.85-0.93)	0.76 (0.73-0.80)	0.85 (0.81-0.89)	0.94 (0.89-0.99)	0.94 (0.89-0.99)	0.94 (0.89-0.99)
2	4248/270420	1.57 (1.52-1.62)	0.93 (0.90-0.97)	0.86 (0.82-0.89)	0.92 (0.88-0.96)	0.99 (0.94-1.03)	0.99 (0.95-1.04)	0.99 (0.95-1.04)
3	4364/271157	1.61 (1.56-1.66)	0.96 (0.92-1.00)	0.90 (0.86-0.94)	0.94 (0.90-0.98)	0.99 (0.95-1.03)	0.99 (0.95-1.04)	0.99 (0.95-1.04)
4	4438/271771	1.63 (1.59-1.68)	0.97 (0.93-1.01)	0.93 (0.89-0.97)	0.96 (0.92-1.00)	0.99 (0.95-1.03)	0.99 (0.95-1.03)	0.99 (0.95-1.03)
5 (richest)	4491/267129	1.68 (1.63-1.73)	ref	ref	ref	ref	ref	ref
			(<0.0001)		(<0.0001)	(0.1409)	(0.1695)	(0.1676)
Maternal occupation								
Gov/Private/Other	1178/68538	1.72 (1.62-1.82)	1.05 (0.99-1.12)	1.13 (1.06-1.20)	1.08 (1.01-1.15)	1.08 (1.01-1.14)	1.08 (1.01-1.15)	1.08 (1.01-1.15)
Self-employed	8527/521463	1.64 (1.60-1.67)	ref	ref	ref	ref	ref	ref
Farming	6230/405711	1.54 (1.50-1.57)	0.94 (0.91-0.97)	0.86 (0.84-0.89)	0.95 (0.91-0.99)	0.97 (0.93-1.01)	0.97 (0.93-1.01)	0.97 (0.93-1.01)
Does not work	5741/361963	1.59 (1.55-1.63)	0.97 (0.94-1.00)	0.93 (0.90-0.96)	0.95 (0.92-0.98)	0.99 (0.96-1.03)	0.99 (0.96-1.03)	0.99 (0.96-1.03)
			(<0.0001)		(<0.0001)	(0.0281)	(0.0234)	(0.0229)

Continued…..

Table A5.5 continued

	Vaccinations / Person days of follow-up	Vaccination Rate / 100 days of follow-up	Unadjusted Rate Ratios RR (95%CI) (p-value)	Rate Ratios adjusted for age-band* aRR (95%CI) (p-value)	Rate Ratios adjusted for distal determinants aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants and birth weight aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants and birth weight & illness aRR (95%CI) (p-value)
Maternal education								
None	6601/436023	1.51 (1.48-1.55)	0.91 (0.89-0.94)	0.81 (0.79-0.84)	0.88 (0.85-0.92)	0.88 (0.84-0.91)	0.88 (0.84-0.91)	0.88 (0.84-0.91)
Primary school	3987/253096	1.58 (1.53-1.62)	0.95 (0.92-0.99)	0.88 (0.85-0.91)	0.92 (0.89-0.96)	0.92 (0.89-0.96)	0.93 (0.89-0.96)	0.93 (0.89-0.96)
Secondary / tertiary	11088/668556	1.66 (1.63-1.69)	ref	ref	ref	ref	ref	ref
			(<0.0001)		(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
Season vaccine due								
Wet	13745/861028	1.60 (1.57-1.62)	ref	ref	ref	ref	ref	ref
Dry	7931/496647	1.60 (1.56-1.63)	1.00 (0.97-1.03)	1.00 (0.97-1.02)	1.00 (0.97-1.02)	1.00 (0.97-1.03)	1.00 (0.97-1.02)	1.00 (0.97-1.02)
			(0.9801)		(0.7435)	(0.8498)	(0.7956)	(0.7494)
Sex								
Male	10974/690763	1.59 (1.56-1.62)	ref	ref	ref	ref	ref	ref
Female	10702/666912	1.60 (1.57-1.64)	1.01 (0.98-1.04)	1.02 (0.99-1.05)	1.02 (0.99-1.05)	1.02 (0.99-1.05)	1.02 (1.00-1.05)	1.02 (1.00-1.05)
			(0.4599)		(0.1589)	(0.1524)	(0.0729)	(0.0804)
Intermediate determinants								
Maternal age (years)								
15 – 19	2436/159626	1.53 (1.47-1.59)	0.94 (0.89-0.98)	0.87 (0.83-0.91)		0.83 (0.78-0.88)	0.84 (0.79-0.89)	0.84 (0.79-0.89)
20 – 24	5533/347342	1.59 (1.55-1.64)	0.98 (0.94-1.01)	0.95 (0.92-0.99)		0.93 (0.89-0.97)	0.93 (0.89-0.97)	0.93 (0.89-0.97)
25 – 29	5872/360350	1.63 (1.59-1.67)	ref	ref		ref	ref	ref
30 – 34	4379/272899	1.60 (1.56-1.65)	0.98 (0.95-1.02)	0.97 (0.93-1.01)		1.02 (0.98-1.07)	1.02 (0.98-1.07)	1.02 (0.98-1.07)
35 years and over	3456/217458	1.59 (1.54-1.64)	0.98 (0.94-1.02)	0.94 (0.91-0.98)		1.02 (0.97-1.07)	1.02 (0.97-1.07)	1.02 (0.97-1.07)
			(0.1036)			(<0.0001)	(<0.0001)	(<0.0001)
Number of children in family								
0-1	6328/392562	1.61 (1.57-1.65)	1.00 (0.97-1.03)	1.00 (0.97-1.03)		1.04 (1.00-1.08)	1.05 (1.01-1.09)	1.05 (1.01-1.09)
2-3	8684/539145	1.61 (1.58-1.64)	ref	ref		ref	ref	ref
4 or more	6664/425968	1.56 (1.53-1.60)	0.97 (0.94-1.00)	0.93 (0.90-0.96)		0.95 (0.92-0.99)	0.95 (0.91-0.99)	0.95 (0.91-0.99)
			(0.1335)			(0.0042)	(0.0008)	(0.0007)
Maternal illness								
No	20612/1291902	1.60 (1.57-1.62)	ref	ref		ref	ref	ref
Yes	1064/65773	1.62 (1.52-1.72)	1.01 (0.95-1.08)	1.02 (0.96-1.09)		1.03 (0.97-1.09)	1.03 (0.97-1.10)	1.03 (0.97-1.10)
			(0.6608)			(0.3891)	(0.3228)	(0.2998)

Continued…..

Table A5.5 continued

	Vaccinations / Person days of follow-up	Vaccination Rate / 100 days of follow-up	Unadjusted Rate Ratios RR (95%CI) (p-value)	Rate Ratios adjusted for age-band* aRR (95%CI) (p-value)	Rate Ratios adjusted for distal determinants aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants and birth weight aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants and birth weight & illness aRR (95%CI) (p-value)
Distance to health facility								
<1.00km	13195/807717	1.63 (1.61-1.66)	ref	ref		ref	ref	ref
1.00-4.99km	5004/313234	1.60 (1.55-1.64)	0.98 (0.95-1.01)	0.95 (0.92-0.98)		0.96 (0.93-0.99)	0.96 (0.93-0.99)	0.96 (0.93-0.99)
>=5.00km	3477/236724	1.47 (1.42-1.52)	0.90 (0.87-0.93)	0.79 (0.76-0.82)		0.87 (0.83-0.90)	0.87 (0.83-0.90)	0.87 (0.83-0.91)
Place of birth			(<0.0001)			(<0.0001)	(<0.0001)	(<0.0001)
Facility	16712/1027355	1.63 (1.60-1.65)	ref	ref		ref	ref	ref
Non-facility	4964/330320	1.50 (1.46-1.55)	0.92 (0.90-0.95)	0.84 (0.81-0.87)		0.94 (0.91-0.97)	0.94 (0.91-0.98)	0.94 (0.91-0.98)
			(<0.0001)			(0.0008)	(0.0014)	(0.0011)
Multiple birth								
No	20902/1308502	1.60 (1.58-1.62)	ref	ref		ref	ref	ref
Yes	774/49173	1.57 (1.47-1.69)	0.99 (0.92-1.06)	0.95 (0.89-1.02)		0.98 (0.91-1.05)	1.08 (1.00-1.17)	1.08 (1.00-1.17)
			(<0.0001)			(0.5596)	(0.0563)	(0.0539)
Proximal Variables								
Birth weight								
>=2.5kg	18427/1145653	1.61 (1.59-1.63)	ref	ref			ref	ref
2.00-2.49kg	2810/181294	1.55 (1.49-1.61)	0.96 (0.93-1.00)	0.92 (0.88-0.96)			0.92 (0.89-0.96)	0.92 (0.89-0.96)
1.50-1.99kg	364/25020	1.45 (1.31-1.61)	0.90 (0.82-1.00)	0.80 (0.72-0.88)			0.76 (0.69-0.85)	0.77 (0.69-0.85)
<1.50kg	75/5708	1.31 (1.05-1.65)	0.82 (0.65-1.02)	0.65 (0.51-0.81)			0.63 (0.50-0.80)	0.64 (0.51-0.80)
			(0.0205)				(<0.0001)	(<0.0001)
Mediating Variables								
Infant illness								
No	2621/169396	1.55 (1.49-1.61)	ref	ref				ref
Yes	19055/1188279	1.60 (1.58-1.63)	0.96 (0.93-1.01)	0.93 (0.89-0.97)				0.94 (0.90-0.98)
			(0.0847)					(0.0028)

** All p-values<0.0001*

Table A5.6: Determinants of DTP3 vaccination between 0 and 22 weeks.

	Vaccinations / Person days of follow-up	Vaccination Rate / 100 days of follow-up	Unadjusted Rate Ratios	Rate Ratios adjusted for age-band*	Rate Ratios adjusted for distal determinants	Rate Ratios adjusted for distal and intermediate determinants	Rate Ratios adjusted for distal and intermediate determinants and birth weight	Rate Ratios adjusted for distal and intermediate determinants and birth weight and illness
			RR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)
Infant age-band (in days)								
<29.5	72/1991481	0.00 (0.00-0.00)	0.00 (0.00-0.00)	_	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
29.5-60.0	7520/580579	1.30 (1.27-1.32)	ref	_	ref	ref	ref	ref
>90.0	7918/319792	2.48 (2.42-2.53)	1.91 (1.85-1.97) (<0.0001)	_	1.96 (1.89-2.02) (<0.0001)	1.97 (1.91-2.04) (<0.0001)	1.97 (1.91-2.04) (<0.0001)	1.97 (1.91-2.04) (<0.0001)
Distal Determinants								
Religion of head of household								
Christian	11351/2002000	0.57 (0.56-0.58)	ref	ref	ref	ref	ref	ref
Muslim	3223/706599	0.46 (0.44-0.47)	0.80 (0.77-0.84)	0.72 (0.70-0.75)	0.80 (0.76-0.84)	0.81 (0.77-0.85)	0.81 (0.77-0.85)	0.81 (0.77-0.85)
None/Traditional/Other	936/183253	0.51 (0.48-0.54)	0.90 (0.84-0.96) (<0.0001)	0.86 (0.81-0.92)	0.93 (0.87-0.99) (<0.0001)	0.95 (0.89-1.02) (<0.0001)	0.95 (0.89-1.01) (<0.0001)	0.95 (0.89-1.01) (<0.0001)
Ethnicity of household								
Akan	7788/1342699	0.58 (0.57-0.59)	ref	ref	ref	ref	ref	ref
Other	7722/1549153	0.50 (0.49-0.51)	0.86 (0.83-0.89) (<0.0001)	0.80 (0.77-0.83)	0.98 (0.94-1.02) (0.3740)	0.98 (0.94-1.02) (0.4456)	0.98 (0.94-1.02) (0.4034)	0.98 (0.94-1.02) (0.4162)
Socioeconomic status								
1 (poorest)	2770/567874	0.49 (0.47-0.51)	0.88 (0.84-0.93)	0.83 (0.79-0.88)	0.96 (0.91-1.02)	1.11 (1.04-1.18)	1.11 (1.04-1.19)	1.11 (1.04-1.19)
2	3074/567966	0.54 (0.52-0.56)	0.98 (0.93-1.03)	0.97 (0.92-1.02)	1.06 (1.00-1.11)	1.17 (1.10-1.23)	1.17 (1.10-1.24)	1.17 (1.11-1.24)
3	3172/575659	0.55 (0.53-0.57)	1.00 (0.95-1.05)	1.00 (0.95-1.05)	1.06 (1.00-1.11)	1.13 (1.07-1.19)	1.13 (1.07-1.19)	1.13 (1.07-1.19)
4	3225/588194	0.55 (0.53-0.57)	0.99 (0.95-1.04)	0.99 (0.94-1.04)	1.03 (0.98-1.09)	1.07 (1.02-1.13)	1.07 (1.02-1.13)	1.07 (1.02-1.13)
5 (richest)	3269/592159	0.55 (0.53-0.57)	ref (<0.0001)	ref	Ref (0.0014)	ref (<0.0001)	ref (<0.0001)	ref (<0.0001)
Maternal occupation								
Gov/Private/Other	891/152741	0.58 (0.55-0.62)	1.08 (1.00-1.15)	1.15 (1.07-1.23)	1.07 (1.00-1.15)	1.06 (0.99-1.14)	1.06 (0.99-1.14)	1.06 (0.99-1.14)
Self-employed	6158/1135396	0.54 (0.53-0.56)	ref	ref	ref	ref	ref	ref
Farming	4408/840165	0.52 (0.51-0.54)	0.97 (0.93-1.01)	0.95 (0.92-0.99)	1.04 (0.99-1.09)	1.07 (1.02-1.12)	1.07 (1.02-1.12)	1.07 (1.02-1.12)
Does not work	4053/763550	0.53 (0.51-0.55)	0.98 (0.94-1.02) (0.0236)	0.98 (0.94-1.02)	0.97 (0.93-1.01) (0.0071)	1.02 (0.98-1.07) (0.0138)	1.02 (0.98-1.07) (0.0143)	1.02 (0.98-1.07) (0.0145)

Continued…..

Table A5.6 continued

	Vaccinations / Person days of follow-up	Vaccination Rate / 100 days of follow-up	Unadjusted Rate Ratios	Rate Ratios adjusted for age-band*	Rate Ratios adjusted for distal determinants	Rate Ratios adjusted for distal and intermediate determinants	Rate Ratios adjusted for distal and intermediate determinants and birth weight	Rate Ratios adjusted for distal and intermediate determinants and birth weight and illness
			RR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)
Maternal education								
None	4349/910019	0.48 (0.46-0.49)	0.82 (0.79-0.85)	0.73 (0.70-0.75)	0.79 (0.75-0.83)	0.79 (0.75-0.82)	0.79 (0.75-0.82)	0.79 (0.75-0.82)
Primary school	2709/537430	0.50 (0.49-0.52)	0.86 (0.82-0.90)	0.79 (0.76-0.82)	0.82 (0.78-0.85)	0.82 (0.79-0.86)	0.82 (0.79-0.86)	0.82 (0.79-0.86)
Secondary / tertiary	8452/1444403	0.59 (0.57-0.60)	ref (<0.0001)	ref	Ref (<0.0001)	ref (<0.0001)	ref (<0.0001)	ref (<0.0001)
Season vaccine due								
Wet	7407/1356296	0.55 (0.53-0.56)	ref	ref	ref	ref	ref	ref
Dry	8103/1535556	0.53 (0.52-0.54)	0.97 (0.94-1.00) (0.0328)	0.96 (0.93-0.99)	0.95 (0.92-0.98) (0.0032)	0.95 (0.92-0.98) (0.0016)	0.95 (0.92-0.98) (0.0013)	0.95 (0.92-0.98) (0.0011)
Sex								
Male	7792/1469759	0.53 (0.52-0.54)	ref	ref	ref	ref	ref	ref
Female	7718/1422093	0.54 (0.53-0.55)	1.02 (0.99-1.06) (0.1446)	1.04 (1.00-1.07)	1.04 (1.00-1.07) (0.0322)	1.04 (1.00-1.07) (0.0270)	1.04 (1.01-1.07) (0.0176)	1.04 (1.01-1.07) (0.0186)
Intermediate Determinants								
Maternal age (years)								
15 – 19	1683/330361	0.51 (0.49-0.53)	0.92 (0.87-0.98)	0.89 (0.84-0.94)		0.80 (0.75-0.86)	0.81 (0.75-0.86)	0.81 (0.75-0.86)
20 – 24	3890/734429	0.53 (0.51-0.55)	0.96 (0.92-1.00)	0.96 (0.92-1.00)		0.92 (0.87-0.96)	0.92 (0.87-0.96)	0.92 (0.87-0.96)
25 – 29	4280/777120	0.55 (0.53-0.57)	ref	ref		ref	ref	ref
30 – 34	3187/585599	0.54 (0.53-0.56)	0.99 (0.94-1.03)	0.98 (0.94-1.03)		1.06 (1.01-1.11)	1.06 (1.01-1.12)	1.06 (1.01-1.12)
35 years and over	2470/464343	0.53 (0.51-0.55)	0.97 (0.92-1.01) (0.0618)	0.94 (0.90-0.99)		1.06 (1.01-1.13) (<0.0001)	1.07 (1.01-1.13) (<0.0001)	1.07 (1.01-1.13) (<0.0001)
Number of living children in family	4563/834703	0.55 (0.53-0.56)	1.00 (0.96-1.03)	1.00 (0.96-1.04)		1.06 (1.01-1.11)	1.06 (1.02-1.12)	1.07 (1.02-1.12)
0-1	6333/1153751	0.55 (0.54-0.56)	ref	ref		ref	ref	ref
2-3	4614/903398	0.51 (0.50-0.53)	0.93 (0.90-0.97) (0.0003)	0.89 (0.86-0.93)		0.89 (0.85-0.93) (<0.0001)	0.88 (0.84-0.93) (<0.0001)	0.88 (0.84-0.93) (<0.0001)
4 or more								
Maternal illness								
No	14754/2749820	0.54 (0.53-0.55)	ref	ref		ref	ref	ref
Yes	756/142032	0.53 (0.50-0.57)	0.99 (0.92-1.07) (0.8301)	0.99 (0.92-1.06)		1.00 (0.93-1.07) (0.9098)	1.00 (0.93-1.07) (0.9731)	1.00 (0.93-1.08) (0.9941)

Continued…..

Table A5.6 continued

	Vaccinations / Person days of follow-up	Vaccination Rate / 100 days of follow-up	Unadjusted Rate Ratios	Rate Ratios adjusted for age-band*	Rate Ratios adjusted for distal determinants	Rate Ratios adjusted for distal and intermediate determinants	Rate Ratios adjusted for distal and intermediate determinants and birth weight	Rate Ratios adjusted for distal and intermediate determinants and birth weight and illness
			RR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)
Distance from health facility								
<1.00km	9606/1743611	0.55 (0.54-0.56)	ref	ref		ref	ref	ref
1.00-4.99km	3694/664652	0.56 (0.54-0.57)	1.01 (0.97-1.05)	1.00 (0.96-1.04)		0.97 (0.93-1.01)	0.97 (0.93-1.01)	0.97 (0.93-1.01)
>=5.00km	2210/483589	0.46 (0.44-0.48)	0.83 (0.79-0.87) (<0.0001)	0.75 (0.72-0.79)		0.78 (0.74-0.83) (<0.0001)	0.79 (0.75-0.83) (<0.0001)	0.79 (0.75-0.83) (<0.0001)
Place of birth								
Facility	12149/2213232	0.55 (0.54-0.56)	ref	ref		ref	ref	ref
Non-facility	3361/678620	0.50 (0.48-0.51)	0.90 (0.87-0.94) (<0.0001)	0.86 (0.82-0.89)		0.96 (0.91-1.00) (0.0399)	0.96 (0.92-1.00) (0.0483)	0.96 (0.92-1.00) (0.0478)
Multiple birth								
No	14983/2788890	0.54 (0.53-0.55)	ref	ref		ref	ref	ref
Yes	527/102962	0.51 (0.47-0.56)	0.95 (0.87-1.04) (0.2709)	0.93 (0.86-1.02)		0.97 (0.89-1.06) (0.5549)	1.05 (0.95-1.15) (0.3567)	1.05 (0.95-1.15) (0.3447)
Proximal Variables								
Birth weight								
>=2.5kg	13238/2452731	0.54 (0.53-0.55)	ref	ref			ref	ref
2.00-2.49kg	1992/378547	0.53 (0.50-0.55)	0.97 (0.93-1.02)	0.96 (0.91-1.00)			0.96 (0.91-1.01)	0.96 (0.91-1.01)
1.50-1.99kg	239/49991	0.48 (0.42-0.54)	0.89 (0.78-1.01)	0.83 (0.73-0.95)			0.80 (0.70-0.92)	0.80 (0.70-0.92)
<1.50kg	41/10583	0.39 (0.29-0.53)	0.72 (0.53-0.98) (0.0246)	0.63 (0.46-0.85)			0.61 (0.45-0.83) (0.0001)	0.61 (0.45-0.83) (0.0001)
Mediating Variables								
Infant illness								
No	13191/2444466	0.54 (0.53-0.55)	ref	ref				ref
Yes	2319/447386	0.52 (0.50-0.54)	0.96 (0.92-1.00) (0.0726)	0.95 (0.91-0.99)				1.03 (0.98-1.08) (0.2933)

** All p-values<0.0001*

Table A*5.7*: Determinants of DTP3 vaccination between 0 and 26 weeks

	Vaccinations / Person days of follow-up	Vaccination Rate / 100 days of follow-up	Unadjusted Rate Ratios RR (95%CI) (p-value)	Rate Ratios adjusted for age-band* aRR (95%CI) (p-value)	Rate Ratios adjusted for distal determinants aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants and birth weight aRR (95%CI) (p-value)	Rate Ratios adjusted for distal and intermediate determinants and birth weight and illness aRR (95%CI) (p-value)
Infant age-band (in days)								
<29.5	72/1991481	0.00 (0.00-0.00)	0.00 (0.00-0.00)	_	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
29.5-60.0	7520/580579	1.30 (1.27-1.32)	ref	_	ref	ref	ref	ref
60.1-90.0	7435/300206	2.48 (2.42-2.53)	1.91 (1.85-1.97)	_	1.95 (1.89-2.02)	1.97 (1.91-2.03)	1.97 (1.91-2.04)	1.97 (1.91-2.04)
>90.0	3374/147403	2.29 (2.21-2.37)	1.77 (1.70-1.84) (<0.0001)	_	1.85 (1.78-1.93) (<0.0001)	1.88 (1.81-1.96) (<0.0001)	1.88 (1.81-1.96) (<0.0001)	1.89 (1.81-1.96) (<0.0001)
Distal Determinants								
Religion of head of household								
Christian	13275/2078786	0.64 (0.63-0.65)	ref	ref	ref	ref	ref	ref
Muslim	4004/748312	0.54 (0.52-0.55)	0.84 (0.81-0.87)	0.73 (0.70-0.75)	0.81 (0.78-0.84)	0.82 (0.79-0.85)	0.82 (0.78-0.85)	0.82 (0.79-0.85)
None/Traditional/Other	1122/192571	0.58 (0.55-0.62)	0.91 (0.86-0.97) (<0.0001)	0.85 (0.80-0.90)	0.92 (0.86-0.98) (<0.0001)	0.94 (0.88-1.00) (<0.0001)	0.94 (0.88-1.00) (<0.0001)	0.94 (0.88-1.00) (<0.0001)
Ethnicity of household	9059/1390660	0.65 (0.64-0.66)	ref	ref	ref	ref	ref	ref
Akan	9342/1629009	0.57 (0.56-0.59)	0.88 (0.86-0.91) (<0.0001)	0.79 (0.77-0.82)	0.97 (0.94-1.01) (0.1798)	0.98 (0.94-1.01) (0.2040)	0.97 (0.94-1.01) (0.1814)	0.97 (0.94-1.01) (0.1889)
Other								
Socioeconomic status								
1 (poorest)	3367/598063	0.56 (0.54-0.58)	0.89 (0.85-0.94)	0.82 (0.79-0.86)	0.95 (0.90-1.00)	1.09 (1.03-1.16)	1.09 (1.03-1.16)	1.09 (1.03-1.16)
2	3624/592986	0.61 (0.59-0.63)	0.97 (0.93-1.02)	0.95 (0.91-0.99)	1.03 (0.98-1.09)	1.14 (1.08-1.20)	1.14 (1.08-1.20)	1.14 (1.08-1.20)
3	3724/599933	0.62 (0.60-0.64)	0.99 (0.94-1.03)	0.98 (0.94-1.03)	1.04 (0.99-1.09)	1.10 (1.05-1.16)	1.11 (1.05-1.16)	1.11 (1.05-1.16)
4	3807/612809	0.62 (0.60-0.64)	0.99 (0.94-1.03)	0.98 (0.93-1.02)	1.02 (0.98-1.07)	1.06 (1.01-1.11)	1.06 (1.01-1.11)	1.06 (1.01-1.11)
5 (richest)	3879/615879	0.63 (0.61-0.65)	ref (<0.0001)	ref	Ref (0.0024)	ref (<0.0001)	ref (0.0001)	ref (0.0001)
Maternal occupation								
Gov/Private/Other	1039/157875	0.66 (0.62-0.70)	1.07 (1.00-1.14)	1.16 (1.09-1.24)	1.09 (1.02-1.16)	1.07 (1.01-1.15)	1.08 (1.01-1.15)	1.07 (1.01-1.15)
Self-employed	7290/1184880	0.62 (0.60-0.63)	ref	ref	ref	ref	ref	ref
Farming	5280/879142	0.60 (0.58-0.62)	0.98 (0.94-1.01)	0.96 (0.92-0.99)	1.05 (1.01-1.10)	1.09 (1.04-1.13)	1.09 (1.04-1.13)	1.09 (1.04-1.13)
Does not work	4792/797772	0.60 (0.58-0.62)	0.98 (0.94-1.01) (0.0323)	0.97 (0.94-1.01)	0.97 (0.93-1.01) (0.0001)	1.02 (0.98-1.06) (0.0006)	1.02 (0.98-1.07) (0.0006)	1.02 (0.98-1.06) (0.0006)

Continued…..

Table A5.7 continued

	Vaccinations / Person days of follow-up	Vaccination Rate / 100 days of follow-up	Unadjusted Rate Ratios	Rate Ratios adjusted for age-band*	Rate Ratios adjusted for distal determinants	Rate Ratios adjusted for distal and intermediate determinants	Rate Ratios adjusted for distal and intermediate determinants and birth weight	Rate Ratios adjusted for distal and intermediate determinants and birth weight and illness
			RR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)
Maternal education								
None	5309/961011	0.55 (0.54-0.57)	0.84 (0.81-0.87)	0.72 (0.70-0.75)	0.78 (0.75-0.82)	0.78 (0.75-0.82)	0.78 (0.75-0.82)	0.78 (0.75-0.82)
Primary school	3291/564140	0.58 (0.56-0.60)	0.89 (0.86-0.93)	0.79 (0.76-0.82)	0.82 (0.79-0.86)	0.83 (0.80-0.87)	0.83 (0.80-0.87)	0.83 (0.80-0.87)
Secondary / tertiary	9801/1494518	0.66 (0.64-0.67)	ref	ref	ref	ref	ref	ref
			(<0.0001)		(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
Season vaccine due								
Wet	8750/1414006	0.62 (0.61-0.63)	ref	ref	ref	ref	ref	ref
Dry	9651/1605663	0.60 (0.59-0.61)	0.97 (0.94-1.00)	0.96 (0.93-0.98)	0.95 (0.92-0.98)	0.95 (0.92-0.98)	0.95 (0.92-0.98)	0.96 (0.92-0.98)
			(0.0487)		(0.0009)	(0.0004)	(0.0003)	(0.0002)
Sex								
Male	9279/1535926	0.60 (0.59-0.62)	ref	ref	ref	ref	ref	ref
Female	9122/1483743	0.61 (0.60-0.63)	1.02 (0.99-1.05)	1.03 (1.00-1.06)	1.03 (1.00-1.06)	1.03 (1.00-1.06)	1.04 (1.01-1.07)	1.04 (1.01-1.07)
			(0.2353)		(0.0359)	(0.0299)	(0.0182)	(0.0191)
Intermediate Determinants								
Maternal age (years)								
15 – 19	2002/346191	0.58 (0.55-0.60)	0.93 (0.88-0.98)	0.88 (0.83-0.93)		0.79 (0.74-0.84)	0.80 (0.75-0.85)	0.80 (0.75-0.85)
20 – 24	4615/767930	0.60 (0.58-0.62)	0.96 (0.93-1.00)	0.95 (0.91-0.98)		0.91 (0.87-0.94)	0.91 (0.87-0.95)	0.91 (0.87-0.95)
25 – 29	5044/808652	0.62 (0.61-0.64)	ref	ref		ref	ref	ref
30 – 34	3789/610837	0.62 (0.60-0.64)	0.99 (0.95-1.04)	0.98 (0.94-1.02)		1.06 (1.02-1.11)	1.07 (1.02-1.11)	1.07 (1.02-1.12)
35 years and over	2951/486059	0.61 (0.59-0.63)	0.97 (0.93-1.02)	0.94 (0.90-0.98)		1.06 (1.01-1.12)	1.06 (1.01-1.12)	1.06 (1.01-1.12)
			(0.0338)			(<0.0001)	(<0.0001)	(<0.0001)
Number of living children in family								
0-1	5363/869266	0.62 (0.60-0.63)	0.99 (0.96-1.03)	1.00 (0.97-1.04)		1.07 (1.02-1.11)	1.07 (1.03-1.12)	1.07 (1.03-1.12)
2-3	7458/1201671	0.62 (0.61-0.63)	ref	ref		ref	ref	ref
4 or more	5580/948732	0.59 (0.57- 0.60)	0.95 (0.92-0.98)	0.90 (0.86-0.93)		0.89 (0.85-0.93)	0.88 (0.85-0.92)	0.88 (0.85-0.92)
			(0.0055)			(<0.0001)	(<0.0001)	(<0.0001)
Maternal illness								
No	17509/2870991	0.61 (0.60-0.62)	ref	ref		ref	ref	ref
Yes	892/148678	0.60 (0.56-0.64)	0.98 (0.92-1.05)	0.97 (0.91-1.04)		0.98 (0.92-1.05)	0.98 (0.92-1.05)	0.98 (0.92-1.05)
			(0.6325)			(0.5530)	(0.6086)	(0.6288)

Continued…

Table A5.7 continued

	Vaccinations / Person days of follow-up	Vaccination Rate / 100 days of follow-up	Unadjusted Rate Ratios	Rate Ratios adjusted for age-band*	Rate Ratios adjusted for distal determinants	Rate Ratios adjusted for distal and intermediate determinants	Rate Ratios adjusted for distal and intermediate determinants and birth weight	Rate Ratios adjusted for distal and intermediate determinants and birth weight and illness
			RR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)	aRR (95%CI) (p-value)
Distance from health facility								
<1.00km	11291/1816583	0.62 (0.61-0.63)	ref	ref		ref	ref	ref
1.00-4.99km	4335/690858	0.63 (0.61-0.65)	1.01 (0.97-1.05)	1.01 (0.97-1.04)		0.98 (0.94-1.01)	0.98 (0.94-1.01)	0.98 (0.95-1.02)
>=5.00km	2775/512228	0.54 (0.52-0.56)	0.87 (0.84-0.91) (<0.0001)	0.77 (0.74-0.80)		0.81 (0.77-0.85) (<0.0001)	0.81 (0.77-0.85) (<0.0001)	0.81 (0.77-0.85) (<0.0001)
Place of birth								
Facility	14336/2305655	0.62 (0.61-0.63)	ref	ref		ref	ref	ref
Non-facility	4065/714014	0.57 (0.55-0.59)	0.92 (0.88-0.95) (<0.0001)	0.85 (0.82-0.88)		0.95 (0.91-0.99) (0.0092)	0.95 (0.91-0.99) (0.0121)	0.95 (0.91-0.99) (0.0120)
Multiple birth								
No	17758/2911766	0.61 (0.60-0.62)	ref	ref		ref	ref	ref
Yes	643/107903	0.60 (0.55-0.64)	0.98 (0.90-1.06) (0.5625)	0.95 (0.88-1.03)		0.99 (0.92-1.07) (0.8520)	1.07 (0.98-1.16) (0.1356)	1.07 (0.98-1.16) (0.1298)
Proximal Variables								
Birth weight								
>=2.5kg	15694/2559854	0.61 (0.60-0.62)	ref	ref			ref	ref
2.00-2.49kg	2360/395994	0.60 (0.57-0.62)	0.97 (0,93-1.01)	0.95 (0.91-0.99)			0.95 (0.91-1.00)	0.95 (0.91-1.00)
1.50-1.99kg	296/52518	0.56 (0.50-0.63)	0.92 (0.82-1.03)	0.86 (0.77-0.96)			0.82 (0.73-0.92)	0.82 (0.73-0.92)
<1.50kg	51/11303	0.45 (0.34-0.59)	0.74 (0.56-0.97) (0.0334)	0.62 (0.47-0.82)			0.60 (0.45-0.79) (<0.0001)	0.60 (0.46-0.79) (<0.0001)
Mediating Variables								
Infant illness								
No	15628/2551511	0.61 (0.60-0.62)	ref	ref				ref
Yes	2773/468158	0.59 (0.57-0.61)	0.97 (0.93-1.01) (0.1027)	0.95 (0.91-0.99)				1.03 (0.99-1.07) (0.1498)

** All p-values<0.0001*

CHAPTER 6: NEONATAL VACCINATION OF LBW INFANTS

Preamble

The paper presented in this chapter addresses PhD objective 3, which is to investigate birth weight and other factors as determinants of neonatal BCG vaccination. ***Section 6.1*** *presents a short overview of the paper.* ***Section 6.2*** *presents the paper itself. In* ***Section 6.3****, I outline some of the issues that I considered when I designed the analysis for the study. In* ***Section 6.4****, I discuss the extent to which the design of the analyses may or may not have biased the associations reported in the paper.*

6.1. INTRODUCTION

In the previous chapter I presented the results of an analysis that investigated whether LBW was a determinant of DTP vaccination in the postneonatal period. In this chapter, I present the results of an analysis to investigate the association between birth weight and neonatal BCG vaccination, and to investigate whether this association varies by place of delivery and infant illness. I used the data from the prospective population-based Neovita cohort to do this analysis. I also investigated other determinants of neonatal BCG vaccination. The study population comprised 22217 infants with known vaccination status who were in follow-up at the end of the neonatal period. The outcomes were odds ratios for BCG vaccination at the end of the neonatal period (0-27 days), calculated using logistic regression, and uptake of BCG vaccination at the end of the neonatal period. Methods to define vaccination status, birth weight and the other exposures of interest are described in **Chapter 3**, as are details on the process of model building. I adjusted all estimates a priori for potential confounders.

6.2. PAPER 3: NEONATAL VACCINATION OF LOW BIRTH WEIGHT INFANTS IN GHANA

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SECTION A – Student Details

Student	Maureen O'Leary
Principal Supervisor	Sara Thomas
Thesis Title	Low birth weight as a risk factor for undervaccination in rural Ghana; evidence from a population based cohort

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Archives of Disease in Childhood
Please list the paper's authors in the intended authorship order:	Maureen O'Leary, Karen Edmond, Sian Floyd, Lisa Hurt, Caitlin Shannon, Gyan Thomas, Sam Newton, Betty Kirkwood, Sara Thomas.
Stage of publication	In peer review

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I developed the idea for this research in collaboration with Sara Thomas and Sian Floyd. This research is based on a secondary analysis of data collected as part of a randomised control trial of neonatal vitamin A supplementation. I was the epidemiologist on the trial and I spent 3 years in Ghana overseeing and ensuring the quality of the data collected for the trial and subsequently included in this research. I cleaned the data and prepared the datasets used in the analyses. I designed the research and developed a detailed plan of analysis, with supervision and input from Sara Thomas and Sian Floyd. Sara Thomas also advised on the sub-group analysis among infants born in health facilities. I wrote the program for the analyses, ran the analyses and drafted the manuscript. Sara Thomas and Karen Edmond provided advice on the interpretation of the results. All co-authors commented on the manuscript. The article was peer-reviewed

Student Signature:  **Date:** 27/7/16

Supervisor Signature:  **Date:** 27/7/16

NEONATAL VACCINATION OF LOW BIRTH WEIGHT INFANTS IN GHANA

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Key Words: *Birth weight, neonatal vaccination, Ghana*

Word count: 2896

ABSTRACT

Objectives:

Global vaccination policy advocates for identifying and targeting groups who are under-served by vaccination to increase equity and uptake. We investigated whether birth weight and other factors are determinants of neonatal BCG vaccination, in order to identify infants under-served by vaccination.

Methods:

We used logistic regression to calculate adjusted odds ratios (AOR) for the association between birth weight (categorised as non-low birth weight (NLBW) (≥2.50kg) and low birth weight (LBW) (2-2.49kg, 1.50-1.99kg and <1.50kg) and non-vaccination with BCG at the end of the neonatal period (0-27 days). We assessed whether this association varied by place of delivery and infant illness. We calculated how BCG timing and uptake would improve by ensuring the vaccination of all facility-born infants prior to discharge.

Results:

There was a strong dose response relationship between LBW and not receiving BCG in the neonatal period (p-trend<0.0001). Infants weighing 1.50-1.99kg had odds of non-vaccination 1.6 times (AOR=1.64; 95%CI:1.30-2.08), and those weighing <1.50kg 2.4 times (AOR=2.42; 95%CI:1.50-3.88) those of NLBW infants. Other determinants included place of delivery, distance to the health facility and socioeconomic status. Neither place of delivery nor infant illness modified the association between birth weight and vaccination (p-interaction all >0.19). Facility-born infants were vaccinated at a mean of 6 days, suggesting they were not vaccinated in the facility at birth but were referred for vaccination.

Conclusions:

LBW is a risk factor for neonatal vaccination, even for facility-born infants. Ensuring vaccination at facility births would substantively improve timing and equitable BCG vaccination.

INTRODUCTION

Approximately 3 in 10 deaths among children aged 1-59 months are vaccine preventable,[1] and one in five infants is not fully vaccinated by age 52 weeks. Substantive socio-demographic inequities in vaccination remain.[2] Many infants are vaccinated late.[3 4] The latest global vaccination policy highlights the need to identify and target those under-served by vaccination, in order to increase equity and uptake.[2]

Using data from a large prospective population-based trial of neonatal vitamin A supplementation in Kintampo in rural Ghana (Neovita), we previously reported that LBW infants are more likely to be delayed in their DTP1 and DTP3 vaccination.[5] For postneonatal vaccines, the onus is on the care-taker to bring the infant for vaccination at scheduled times. Any vaccination delay may be partly due to care-taker hesitancy to bring infants for vaccination, possibly due to their fragility or illness.[6] This may not be the case for neonatal vaccinations, as the large proportion of facility-born infants automatically have opportunities for vaccination. Consequently, vaccine determinants may differ in these periods. In an effort to identify further those under-served by vaccination, we investigated birth weight and other factors as determinants of neonatal vaccination.

In countries with a high prevalence of tuberculosis, the World Health Organisation (WHO) recommends "BCG be given to all healthy neonates, or as soon as possible after birth".[7] In addition to BCG, in Ghana, a birth dose of polio (OPVB) is recommended at a maximum age of two weeks,[8] as part of a four dose schedule. Hepatitis B is not given in Ghana until six weeks of age. The WHO recommends BCG vaccination by intradermal injection to the arm,[7] whereas OPVB is given orally.[9] We selected BCG as an indicator for neonatal vaccination due to its longer recommended window for administration (throughout the neonatal period), and on the basis that any hesitancy relating to the vaccination of fragile infants would be more evident for injected vaccines.

Low birth weight is not a contraindication to BCG vaccination. [7] The WHO advises that infants should receive all due vaccines prior to discharge from health facilities.[10] Therefore, infants born in health facilities should be vaccinated prior to discharge home.

Infant illness has been cited as a reason for non-vaccination by both caregivers and vaccine-providers.[6] Given this, and the opportunities for vaccination associated with being born in a

facility, as secondary objectives we investigated whether the association between birth weight and neonatal BCG vaccination varied by place of delivery and infant illness.

MATERIALS AND METHODS

Neovita was undertaken at the Kintampo Health Research Centre (KHRC) in rural Ghana. Trial methods have been described in detail elsewhere.[11 12]

In Ghana, neonatal vaccines are given either at the health facility following delivery, or at child health clinics in health facilities or Community Health Planning System (CHPS) compounds in the community. Monthly mobile outreach clinics target areas lacking health facilities or CHPS compounds. Following vaccination, the vaccine provider records (on a vaccination card, or less commonly, in the mother's antenatal card) the administrated vaccine, the batch-number, date, and clinic name.

Infants who were up to three days of age at screening, who could suckle or feed, and who were staying in the study area for at least six months after enrolment were included in the trial.

Trained field workers used a prospective surveillance system (that monitored registered women aged 15-49 years for pregnancies and deliveries) to ascertain all births in the study area between August 2010 and November 2011. They enrolled eligible infants of consenting mothers in the trial and weighed them using calibrated electronic (38%) or spring (62%) scales. They recorded birth weights to the nearest 0.1kg (electronic scales) or 0.2kg (spring scales). All but five infants (0.2%) were weighed within 72 hours of delivery. At enrolment, field workers collected data on infant, maternal and household characteristics. Data on vaccination status (written record and maternal recall) were collected at monthly follow-up visits.

Infants were categorised as a) vaccinated, known vaccination date (if they had a plausible vaccination date on their vaccination card); b) vaccinated, unknown vaccination date (if they had an unknown or implausible date on their card); and c) unvaccinated (if either i) their card was viewed and had no evidence of vaccination, or ii) their card was not viewed (possibly because they did not have a card) but their caretaker consistently reported that they had never been vaccinated). In addition, infants whose card was never viewed and whose mothers reported they were vaccinated, but did not report which vaccine they

received, were categorised as vaccination status unknown, as were those infants never seen in follow-up, with no information on their vaccination status.

We categorised infants as either non-low birth weight (NLBW) (weighing ≥2.50kg) or low birth weight (LBW) (2.00-2.49kg, 1.50-1.99kg, and <1.50kg). Neonatal illness was a health facility admission in the neonatal period (0-27 days of age).

Infants with known vaccination status, in follow-up at the end of the neonatal period, and having complete covariate data were eligible for inclusion in the analyses.

Analytical methods

We conducted all analyses using STATA 14.1 (STATACORP, 2015). As neonatal BCG vaccination is a frequent event, we calculated adjusted odds ratios (AOR) for the less frequent outcome of non-vaccination (rather than for vaccination) using multivariable logistic regression. The resulting AORs for this less frequent outcome thus approximated more closely to risk or rate ratios. Model building was informed by a hierarchical framework[5] of the determinants of vaccination identified a priori.[3 4 13 14] We initially fit a model comprising distal determinants (religion, ethnicity, socioeconomic status, maternal occupation, maternal education, vaccine due in wet season, infant sex), then added intermediate determinants (maternal age/ family size, maternal illness in the year before delivery, distance to the nearest health facility, place of delivery, multiple birth), followed by birth weight, and finally infant illness, a possible mediator of the association between birth weight and vaccination. We used likelihood ratio tests and 95% confidence intervals (95%CI) to assess statistical associations between each explanatory variable and vaccination.

We fitted interaction terms of birth weight and i) place of delivery, and ii) neonatal illness to the final model to assess whether either of these modified the association between birth weight and vaccination.

For all infants, irrespective of place of birth, we calculated BCG uptake rates at the end of the neonatal period and at 8, 12 and 52 weeks of age, stratified by birth weight, to examine variation by time since the due date. To assess how ensuring vaccination of facility-born infants prior to discharge would affect vaccination, we calculated 'theoretical' proportions vaccinated by assigning these infants as vaccinated in the neonatal period. We calculated the proportional increase in vaccination by dividing the theoretical proportion by the actual proportion for each time-period.

The ethics committees of the World Health Organisation (WHO), the London School of Hygiene & Tropical Medicine (LSHTM) and the KHRC granted approval for the Neovita trial. The Bill and Melinda Gates Foundation funded the Neovita trial.

RESULTS

Of 22955 infants enrolled in Neovita, 22217 (96.8%) were included in the analyses. Among 738 excluded, 362 were BCG vaccination status unknown, 242 were BCG vaccinated with an unknown date, 88 were lost-to-follow up in the neonatal period, and 46 were missing covariate data. In total 275 of the 738 excluded infants died in the neonatal period. Table 1 shows that excluded infants were more likely to have LBW, to live further from a health facility, to be a multiple birth and to have poorer mothers.

Infants were BCG vaccinated at a median of 8 days; 77% were vaccinated by the end of the neonatal period. Uptake decreased with declining birth weight, and was lowest (60%) among infants weighing <1.50kg. There was a strong dose-response relationship between LBW and the odds of non-vaccination in the neonatal period (p-trend<0.0001), after adjustment for other variables (Table 2). Infants weighing 1.50-1.99kg (AOR=1.64; 95%CI:1.30-2.08) and those weighing <1.50kg (AOR=2.42; 95%CI:1.50-3.88) had odds of non-vaccination 1.6 times and 2.4 times those of NLBW infants.

Table 1: Baseline characteristics of infants included in the analyses of determinants of neonatal BCG vaccination.

Variable	Excluded Total=738	Included Total = 22217
Distal Determinants		
Religion of head of household		
Christian	471 (63.8)	15508 (69.8)
Muslim	201 (27.2)	5310 (23.9)
None/Traditional/Other	66 (8.9)	1399 (6.3)
Ethnicity		
Akan	317 (43.0)	10376 (46.7)
Non-Akan	421 (57.0)	11841 (53.3)
Socioeconomic status		
1 (poorest)	185 (25.1)	4325 (19.5)
2	174 (23.6)	4376 (19.7)
3	150 (20.3)	4433 (20.0)
4	125 (16.9)	4519 (20.3)
5(richest)	103 (14.0)	4564 (20.5)
Missing Values	1 (0. 1)	
Maternal occupation		
Gov/Private/ Other	31 (4.2)	1194 (5.4)
Self-employed	232 (31.4)	8714 (39.2)
Farming	251 (34.0)	6420 (28.9)
Does not work	224 (30.4)	5889 (26.5)
Maternal education		
None	264 (35.8)	6863 (30.9)
Primary school	138 (18.7)	4098 (18.5)
Secondary / tertiary	322 (43.6)	11256 (50.7)
Missing Values	14 (1.9)	
Vaccine due in wet season	461 (62.5)	14494 (65.2)
Sex, Female	340 (46.1)	10966 (49.4)
Intermediate Determinants		
Maternal age / Family size		
<20 years	114 (15.4)	2531 (11.3)
20-29, 1-3 children	263 (35.6)	7815 (35.2)
20-29, ≥4 children	120 (16.3)	3843 (17.3)
≥30, 1-3 children	29 (3.9)	1108 (5.0)
≥30, ≥4 children	182 (24.7)	6920 (31.2)
Missing Values	30 (4.1)	
Maternal illness in year before delivery	32 (4.3)	1091 (4.9)
Distance		
<1.00km	409 (55.5)	13471 (60.6)
1.00-4.99km	152 (20.6)	5133 (23.1)
>=5.00km	174 (23.6)	3613 (16.3)
Missing Values	2 (0.3)	
Facility delivery	517 (70.1)	17064 (76.8)
Multiple birth	52 (7.1)	795 (3.6)
Proximal Variables		
Birth weight		
>=2.5kg	520 (70.5)	18841 (84.8)
2.00-2.49kg	121 (16.4)	2910 (13.1)
1.50-1.99kg	59 (8.0)	385 (1.7)
<1.50kg	36 (4.8)	81 (0.4)
Missing Values	2 (0.3)	
Mediating Variables		
Neonatal illness	31 (4.2)	426 (1.9)

Table 2: Determinants of non-vaccination with BCG in the neonatal period

	Not Vaccinated / Total	Proportion not vaccinated (95%CI)	Unadjusted Odds Ratios	Adjusted for distal determinants	Adjusted for distal & intermediate determinants	Adjusted for distal, intermediate & proximal determinants (final model)	Final model adjusted for mediating effects of infant illness	Final model among infants born in a health facility
			OR (95%CI) (p-value)	AOR (95%CI) (p-value)	AOR (95%CI) (p-value)	AOR (95%CI) (p-value)	AOR (95%CI) (p-value)	AOR (95%CI) (p-value)
Distal Variables								
Religion of head of household	3387/15508	21.8 (21.2-22.5)	Ref	Ref	Ref	Ref	Ref	Ref
Christian	1310/5310	24.7 (23.5-25.8)	1.17 (1.09-1.26)	1.04 (0.95-1.13)	1.01 (0.93-1.10)	1.01 (0.93-1.11)	1.01 (0.93-1.11)	1.00 (0.89-1.11)
Muslim	392/1399	28.0 (25.7-30.4)	1.39 (1.23-1.58)	0.96 (0.85-1.09)	0.90 (0.79-1.03)	0.90 (0.79-1.03)	0.90 (0.79-1.03)	0.86 (0.72-1.03)
None/Traditional/Other			(<0.0001)	(0.5416)	(0.2438)	(0.2445)	(0.2439)	(0.2440)
Ethnicity								
Akan	1891/10376	18.2 (17.5-19.0)	Ref	Ref	Ref	Ref	Ref	Ref
Non-Akan	3198/11841	27.0 (26.2-27.8)	0.60 (0.56-0.64)	0.91 (0.84-0.99)	0.94 (0.86-1.02)	0.93 (0.86-1.02)	0.93 (0.86-1.02)	0.96 (0.87-1.06)
			(<0.0001)	(0.0320)	(0.1381)	(0.1112)	(0.1099)	(0.4092)
Socioeconomic status								
1 (poorest)	1618/4325	37.4 (36.0-38.9)	5.19 (4.63-5.82)	3.90 (3.42-4.44)	2.70 (2.35-3.10)	2.69 (2.34-3.08)	2.68 (2.33-3.08)	2.98 (2.53-3.50)
2	1271/4376	29.0 (27.7-30.4)	3.56 (3.17-3.99)	2.91 (2.57-3.29)	2.33 (2.05-2.65)	2.32 (2.04-2.64)	2.32 (2.04-2.64)	2.34 (2.03-2.71)
3	1020/4433	23.0 (21.8-24.3)	2.60 (2.31-2.92)	2.27 (2.01-2.57)	1.98 (1.75-2.24)	1.98 (1.74-2.24)	1.98 (1.74-2.24)	1.98 (1.72-2.26)
4	709/4519	15.7 (14.7-16.8)	1.62 (1.43-1.83)	1.50 (1.32-1.70)	1.42 (1.25-1.61)	1.41 (1.24-1.60)	1.41 (1.24-1.60)	1.47 (1.28-1.68)
5 (richest)	471/4564	10.3 (9.5-11.2)	Ref	Ref	Ref	Ref	Ref	Ref
			(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)*	(<0.0001)
Maternal occupation								
Gov/Private/Other	158/1194	13.2 (11.4-15.3)	0.73 (0.61-0.87)	0.89 (0.75-1.07)	0.92 (0.76-1.10)	0.91 (0.76-1.09)	0.91 (0.76-1.10)	0.92 (0.75-1.12)
Self-employed	1500/8714	17.2 (16.4-18.0)	Ref	Ref	Ref	Ref	Ref	Ref
Farming	2082/6420	32.4 (31.3-33.6)	2.31 (2.14-2.49)	1.33 (1.22-1.46)	1.21 (1.11-1.33)	1.21 (1.11-1.33)	1.21 (1.11-1.33)	1.24 (1.11-1.39)
Does not work	1349/5889	22.9 (21.9-24.0)	1.43 (1.32-1.55)	1.19 (1.09-1.30)	1.13 (1.03-1.24)	1.13 (1.03-1.24)	1.13 (1.03-1.24)	1.18 (1.06-1.32)
			(<0.0001)	(<0.0001)	(0.0001)	(0.0001)	(0.0001)	(0.0001)
Maternal education								
None	2032/6863	29.6 (28.5-30.7)	1.95 (1.81-2.09)	1.13 (1.03-1.24)	1.15 (1.05-1.26)	1.15 (1.05-1.27)	1.15 (1.05-1.27)	1.13 (1.01-1.27)
Primary school	1057/4098	25.8 (24.5-27.2)	1.61 (1.48-1.75)	1.18 (1.08-1.29)	1.17 (1.07-1.28)	1.17 (1.06-1.28)	1.17 (1.06-1.28)	1.17 (1.05-1.31)
Secondary / tertiary	2000/11256	17.8 (17.1-18.5)	Ref	Ref	Ref	Ref	Ref	Ref
			(<0.0001)	(0.0013)	(0.0013)	(0.0015)	(0.0015)	0.0138
Vaccine due in wet season	3272/14494	22.6 (21.9-23.3)	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1817/7723	23.5 (22.6-24.5)	1.06 (0.99-1.13)	1.04 (0.97-1.11)	1.04 (0.97-1.12)	1.04 (0.97-1.12)	1.04 (0.97-1.12)	1.05 (0.97-1.15)
No			(0.1082)	(0.2274)	(0.2284)	(0.2353)	(0.2402)	0.2121
Sex								
Male	2701/11251	24.0 (23.2-24.8)	Ref	Ref	Ref	Ref	Ref	Ref
Female	2388/10966	21.8 (21.0-22.6)	0.88 (0.83-0.94)	0.87 (0.82-0,93)	0.86 (0.80-0.92)	0.85 (0.80-0.91)	0.85 (0.80-0.91)	0.83 (0.77-0.90)
			(0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)

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	Not Vaccinated / Total	Proportion not vaccinated (95%CI)	Unadjusted Odds Ratios	Adjusted for distal determinants	Adjusted for distal & intermediate determinants	Adjusted for distal, intermediate & proximal determinants (final model)	Final model adjusted for mediating effects of infant illness	Final model; among infants born in a health facility
			OR (95%CI) (p-value)	AOR (95%CI) (p-value)	AOR (95%CI) (p-value)	AOR (95%CI) (p-value)	AOR (95%CI) (p-value)	AOR (95%CI) (p-value)
Intermediate Variables								
Maternal age / Family size								
<20 years	650/2531	25.7 (24.0-27.4)	1.10 (98.8-1.22)		1.22 (1.07-1.39)	1.19 (1.04-1.35)	1.19 (1.04-1.35)	1.27 (1.09-1.48)
20-29, 1-3 children	1601/7815	20.5 (19.6-21.4)	0.82 (0.76-0.88)		1.10 (1.01-1.20)	1.09 (1.00-1.19)	1.09 (1.00-1.19)	1.09 (0.98-1.22)
20-29, ≥4 children	1008/3843	26.2 (24.9-27.6)	1.13 (1.03-1.24)		1.11 (1.01-1.22)	1.11 (1.10-1.22)	1.11 (1.01-1.22)	1.14 (1.01-1.29)
≥30, 1-3 children	173/1108	15.6 (13.6-17.9)	0.59 (0.50-0.70)		0.93 (0.77-1.11)	0.92 (0.76-1.10)	0.92 (0.76-1.10)	0.97 (0.78-1.19)
≥30, ≥4 children	1657/6920	23.9 (23.0-25.0)	Ref		Ref	Ref	Ref	Ref
			(<0.0001)		(0.0080)	(0.0186)	(0.0191)	(0.0194)
Maternal illness in year before delivery	4840/21126	22.9 (22.3-23.5)	Ref		Ref	Ref	Ref	Ref
No	249/1091	22.8 (20.4-25.4)	1.00 (0.86-1.15)		0.94 (0.80-1.09)	0.93 (0.80-1.08)	0.93 (0.80-1.08)	0.92 (0.76-1.11)
Yes			(0.9468)		(0.3866)	(0.3568)	(0.3545)	(0.3764)
Distance from health facility								
<1.00km	2570/13471	19.1 (18.4-19.8)	Ref		Ref	Ref	Ref	Ref
1.00-4.99km	1146/5133	22.3 (21.2-23.5)	1.22 (1.13-1.32)		1.06 (0.98-1.16)	1.06 (0.98-1.15)	1.06 (0.98-1.15)	1.06 (0.96-1.17)
>=5.00km	1373/3613	38.0 (36.4-39.6)	2.60 (2.40-2.82)		1.37 (1.25-1.50)	1.37 (1.25-1.49)	1.37 (1.25-1.49)	1.60 (1.41-1.81)
			(<0.0001)		(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
Place of birth								
Facility	3079/17064	18.0 (17.5-18.6)	Ref		Ref	Ref	Ref	
Non-facility	2010/5153	39.0 (37.7-40.3)	2.90 (2.71-3.11)		1.83 (1.69-1.98)	1.82 (1.69-1.98)	1.83 (1.69-1.98)	
			(<0.0001)		(<0.0001)	(<0.0001)	(<0.0001)	
Multiple birth								
No	4898/21422	22.9 (22.3-23.4)	Ref		Ref	Ref	Ref	Ref
Yes	191/795	24.0 (21.2-27.1)	1.07 (0.90-1.26)		1.08 (0.91-1.29)	0.93 (0.78-1.13)	0.93 (0.78-1.13)	1.00 (0.81-1.23)
			(0.4468)		(0.3692)	(0.4742)	(0.4747)	(0.9889)
Proximal Variables								
Birth weight								
>=2.5kg	4204/18841	22.3 (21.7-22.9)	Ref			Ref	Ref	Ref
2.00-2.49kg	737/2910	25.3 (23.8-26.9)	1.18 (1.08-1.29)			1.08 (0.98-1.19)	1.08 (0.98-1.19)	1.12 (0.99-1.27)
1.50-1.99kg	116/385	30.1 (25.7-34.9)	1.50 (1.20-1.87)			1.64 (1.30-2.08)	1.64 (1.30-2.08)	1.69 (1.28-2.22)
<1.50kg	32/81	39.5 (29.4-50.6)	2.27 (1.45-3.55)			2.41 (1.50-3.88)	2.42 (1.51-3.89)	2.29 (1.35-3.90
			(<0.0001)			(<0.0001)	(<0.0001)*	(0.0001)
Mediating Variable								
Neonatal illness								
No	5009/21791	23.0 (22.4-23.5)	Ref				Ref	Ref
Yes	80/426	18.8 (15.3-22.8)	0.77 (0.61-0.99)				0.91 (0.71-1.17)	0.89 (0.66-1.20)
			(0.0363)				(0.4627)	(0.4542)

** p-trend = <0.0001*

Not being born in a health facility (compared to being born in a health facility), living 5km or more from the nearest health facility (compared to living within 1km of a health facility), and being in the lowest quintile of socioeconomic status (SES) (compared to the highest) were all strongly associated with not receiving BCG in the neonatal period (Table 2). Almost 40% of home-born infants were BCG unvaccinated, and their odds of non-vaccination were 1.82 times those of facility-born infants (AOR=1.82; 95%CI:1.69-1.98; p=<0.0001). Infants living >5km from a health facility had odds of non-vaccination 1.37 those of infants living within 1km (AOR=1.37; 95%CI:1.25-1.49; p=<0.0001), even after adjusting for place of birth and other factors. A strong dose response relationship was observed between SES and neonatal BCG vaccination (p-trend <0.0001), with infants from the poorest quintile of SES having odds of non-vaccination 2.7 times greater than those from the wealthiest quintile (AOR=2.69; 95%CI:2.34-3.08) even after adjustment for all other explanatory variables.

Having a mother who was a farmer or unemployed (compared to being self-employed), who had primary school education or no education (compared to secondary/tertiary education) and who was less than 20 years of age (compared to being aged 30 or more with four or more children) were associated with an increased odds of non-vaccination in the final model. Conversely, female infants had lower odds of non-vaccination (Table 2).

There was little variation in the effect size for the distal factors after adjustment for intermediate and proximal mediating variables, and in the effect size for intermediate level factors after adjustment for birth weight. Illness did not appear to mediate the effect of birth weight or any other determinants of vaccination (Table 2).

There was little evidence that either place of delivery or infant illness modified the association between birth weight and vaccination (p-value for interaction all >0.2).

Additional analyses of the vaccination of facility-born infants

As a post-hoc analysis we further explored the vaccination of facility-born infants. We analysed their age at vaccination, and analysed their determinants of vaccination.

Facility-born infants were vaccinated at a median age of 6 days (IQR=17). The effect estimates for the determinants of vaccination were very similar to those for the entire study population. The biggest change in effect size was for infants living >5km from a health facility, (AOR=1.60; 95%CI:1.41-1.81) (Table 2).

Impact of vaccinating all facility-born infants before discharge

Overall BCG uptake was 77.1% (95%CI:76.5-77.6) by the end of the neonatal period, 91.8% (95%CI:91.4-92.1) by 8 weeks of age, 95.9% (95%CI:95.6-96.1) by 12 weeks of age, and 98.7% (95%CI:98.5-98.8) by 52 weeks of age (Table 3). At each of these time points, uptake declined with decreasing birth weight, although there was little difference at age 52 weeks (Table 3). We calculated that 91.0% (95%CI:90.6-91.3) of all infants, 91.2% (95%CI:87.9-93.6) of infants weighing 1.50-1.99kg, and 88.9% (95%CI:79.9-94.1) of infants weighing <1.50kg may have been vaccinated in the neonatal period if all facility-born infants were vaccinated prior to discharge. This represented a respective 18%, 31% and 47% increase in vaccine uptake by the end of the neonatal period. Similar smaller gains in vaccine uptake would have occurred for the other categories of birth weight (Table 3).

Table 3: BCG uptake rates at 4, 8, 12 and 52 weeks of age by birth weight, and rates that could be achieved if all those born in a facility had been vaccinated prior to discharge from the facility.

	BCG Uptake Rates		
Birth weight	**Actual**	**Theoretical**	**% Increase in Vaccine Uptake**
		Age 4 weeks	
>=2.5kg	77.7 (77.1-78.3)	91.2 (90.8-91.6)	17.4
2.00-2.49kg	74.7 (73.1-76.2)	89.4 (88.2-90.5)	19.7
1.50-1.99kg	69.9 (65.1-74.3)	91.2 (87.9-93.6)	30.5
<1.50kg	60.5 (49.4-70.6)	88.9 (79.9-94.1)	46.9
Overall	77.1 (76.5-77.6)	91.0 (90.6-91.3)	18.0
		Age 8 weeks	
>=2.5kg	92.1 (91.7-92.5)	96.7 (96.4-96.9)	5.0
2.00-2.49kg	90.4 (89.3-91.4)	95.7 (94.9-96.4)	5.9
1.50-1.99kg	87.5 (83.8-90.5)	97.9 (95.9-99.0)	11.9
<1.50kg	72.8 (62.1-81.4)	91.4 (82.9-95.8)	25.5
Overall	91.8 (91.4-92.1)	96.5 (96.3-96.8)	5.1
		Age 12 weeks	
>=2.5kg	96.1 (95.8-96.4)	98.2 (98.1-98.4)	2.2
2.00-2.49kg	95.1 (94.2-95.8)	97.8 (97.2-98.2)	2.8
1.50-1.99kg	93.8 (90.9-95.8)	98.4 (96.6-99.3)	4.9
<1.50kg	88.9 (79.9-94.1)	97.5 (90.6-99.4)	9.7
Overall	95.9 (95.6-96.1)	98.2 (98.0-98.4)	2.4
		Age 52 weeks	
>=2.5kg	98.8 (98.6-98.9)	99.5 (99.4-99.6)	0.1
2.00-2.49kg	98.1 (97.5-98.5)	99.1 (98.7-99.4)	1.0
1.50-1.99kg	97.4 (95.2-98.6)	99.5 (97.9-99.9)	2.2
<1.50kg	96.3 (89.1-98.8)	98.8 (91.7-99.8)	2.6
Overall	98.7 (98.5-98.8)	99.4 (99.3-99.5)	0.7

DISCUSSION

Our analyses indicate that LBW infants are at high risk of missing BCG vaccination in the neonatal period. There appears to be a dose-response relationship between vaccination and birth weight; vaccination declines with decreasing birth weight, regardless of place of birth.

We excluded sicker weaker infants who were unable to feed at enrolment, as well as those who died during the neonatal period. The LBW infants included in our analyses were probably well, and illness was probably not a contraindication to vaccination. Our finding that neonatal illness did not appear to mediate the association between birth weight and vaccination, overall or when stratified by place of delivery, supports this. LBW is not a contraindication to vaccination, and LBW infants are recommended to be vaccinated at the same chronological age as NLBW infants;[15] however, our results indicate that this recommendation is not being optimally adhered to in Ghana.

We identified a number of additional determinants of neonatal BCG vaccination, including place of delivery, distance to health facility, SES, and maternal education, occupation and age. These were also identified as determinants in our analyses of postneonatal vaccination,[5] and other analyses,[16] and reflect broader inequities in access to care in our study population.

In our study area, > 20% of the 77% of facility-born infants were unvaccinated at the end of the neonatal period, demonstrating a lack of compliance with the routine schedule. This was double for infants weighing <1.5kg at birth.

Vaccination was even lower among home-born infants, suggesting parental delay in accessing vaccination services, or for those living far from a facility, the monthly scheduling of mobile outreach clinics. The fact that home-born LBW infants are even more delayed may reflect parental reluctance to bring fragile infants for vaccination, as previously documented in a review of unpublished surveys.[6]

Facility-born infants were vaccinated at a median age of six days, suggesting that many are unvaccinated at discharge following delivery and that they may instead be referred to the child health clinic for vaccination. This would explain why birth weight and other maternal and household factors remain as vaccine determinants among facility-born infants. If true, then this practice is allowing inequities in vaccination to persist. A single vial of BCG vaccinates twenty infants. Fear of wastage has previously been cited as a reason for missing opportunities for vaccination,[17] and may be a motivation for referring facility-born infants to the child health clinic for vaccination.

Overall uptake of BCG vaccination at age 52 weeks was high; however, many infants were vaccinated late, including a higher proportion of LBW infants. BCG vaccination is known to have an important protective effect against TB meningitis in the first five years of life[18].

Timely vaccination is important so as not to prolong the risk of infection. Furthermore, timeliness of vaccination is increasingly recognised as an important indicator of the overall quality of vaccination programmes[19], and our finding that LBW infants were less likely to be in compliance with the routine schedule, highlights them as a group who are under-served by vaccination. The Global Vaccine Action Plan[2] advocates for identifying groups who are under-served by routine vaccination services so that they can be targeted for vaccination, and so that inequities in the delivery of the vaccination programme can be reduced. Ensuring vaccination of facility-born infants prior to discharge would optimise compliance with the recommended schedule and the timeliness of BCG vaccination.

Our finding of reduced vaccination of LBW infants is consistent with our previous finding of delayed postneonatal vaccination (with DTP1 and DTP3) of LBW infants.[5]. It also supports recent findings[20] from Nairobi Kenya, that infants weighing <2.00kg living in informal urban settlements took 9 times longer to be vaccinated in the first 90 days of life than NLBW infants. The difference in the magnitude of the association between our study and the Kenyan study may be due to the exclusion of unvaccinated infants, the lower prevalence of LBW (6%), the higher proportion of facility-born infants (96%), and the higher proportion of private facility-born infants (67%) in the Kenyan study.

Data from Guinea Bissau[21] also suggested lower BCG vaccination among LBW infants. As there was reportedly a national policy of delaying vaccination of LBW infants until they had gained weight or attended for DTP vaccination, these results are not generalisable to countries, such as Ghana, where no such policy exists.

A study from Nigeria[22] reported delayed vaccination of under-nourished children. This study provides indirect evidence of the effect of birth weight, in addition to infant feeding and illness (the causes of undernourishment[23]) on BCG vaccination.

Strengths

Our study was strengthened by low loss to follow-up rates (<3%), by the population-based nature of the sample and by the collection of high quality data on both birth weight and vaccination.

Limitations

We lacked qualitative data on the practices associated with vaccination following delivery, including the reasons why infants born in health facilities were not getting vaccinated, and why LBW infants born in health facilities were less likely to be vaccinated. This limits our

understanding of the barriers to neonatal vaccination (among both facility-born and home-born infants), and to the vaccination of LBW infants.

A large number of variables were included in our models, thus increasing the possibility of type-1 errors. Due to small numbers, our study was underpowered to detect differences in analyses where birth weight was stratified by factors such as infant illness. Although we demonstrated that vaccinating all facility-born infants prior to discharge could substantively improve the timing and equity of delivery of BCG vaccination, this finding may not be generalizable to settings where most infants are born at home.

CONCLUSIONS

Our analyses indicate that LBW is a risk factor for not being vaccinated with BCG in the neonatal period, even for facility-born LBW infants. Efforts to improve neonatal vaccination, especially for LBW infants, are warranted, regardless of where they are born. For LBW infants born in facilities, vaccination prior to discharge is recommended. Qualitative studies to understand the reasons for non-vaccination with BCG in the neonatal period are needed. In particular studies are needed to understand why infants, including LBW infants born in health facilities are not getting vaccinated.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Delayed BCG vaccination was associated with low birth weight (LBW) among primarily facility born infants in urban slums in Kenya.

Undernourishment (caused by LBW, illness and feeding practices) was also associated with delayed BCG vaccination in urban Nigeria.

WHAT THIS STUDY ADDS

This large, generalisable prospective population-based cohort study in rural Ghana demonstrates lower compliance with the BCG vaccination schedule among LBW compared to non-LBW infants.

LBW is a strong determinant of neonatal BCG vaccination, with a dose response relationship between birth weight and vaccination.

The association persists even for facility-born LBW infants, suggesting a lack of compliance with policy to vaccinate prior to discharge from the facility.

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CONTRIBUTIONS

MOL drafted the report, and it was reviewed by all authors. MOL, ST, SF, and KE designed the study and analyses. KE, BK, and SN designed the trial. CS, MOL, GT, SN, LH, and KE were responsible for trial conduct. GT coordinated the fieldwork. MOL and CS managed the database. MOL undertook the statistical analyses with input from ST and SF.

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6.3. CONSIDERATIONS IN THE CHOICE OF ANALYTICAL METHODOLOGY

Whereas in my analysis of postneonatal vaccination I calculated vaccination rates in specific risk periods, in this analysis I measured vaccine uptake by the end of the neonatal period. As outlined above, the BCG schedule allows for vaccination at any time within the neonatal period[1]. Therefore, an infant vaccinated on the last day of the neonatal period would still comply with the schedule. Defining the risk periods from the vaccine due date (as I did for the analyses of postneonatal vaccination) would not have allowed an assessment of neonatal vaccination. Given this, I measured overall compliance with the schedule at the end of the neonatal period, rather than analysing vaccination rate ratios within or starting at the end of the neonatal period.

As BCG vaccination is a common event in the neonatal period, I presented odds ratios for (less-common) non-vaccination as they would be a better approximation of the risk ratios for any association between birth weight and the other determinants and vaccination[2].

6.4. DID MEASURING BCG UPTAKE AT THE END OF THE NEONATAL PERIOD BIAS THE ESTIMATES OF THE ASSOCIATION BETWEEN BIRTH WEIGHT AND NEONATAL VACCINATION?

As discussed in **Section 1.4** studies measuring vaccine uptake at pre-defined time-points typically exclude individuals whose follow-up is censored before that time point. Infants who were unvaccinated at the time they were lost to follow-up, and who were lost to follow-up before the time-point, could have been vaccinated between the time they exited the study and the time the outcome was measured. I could not know for sure that they were still unvaccinated at the time the outcome was measured, and so their vaccination status was essentially unknown. These infants would automatically be excluded from the analyses. This would not be the case for vaccinated infants whose vaccination status was known. In order to avoid preferentially including vaccinated infants in the analysis of vaccine uptake at the end of the neonatal period, I decided to only include infants who were still in follow-up at that time point, as I had complete data on the vaccination status of all of these infants.

If infants excluded from the analyses differed to those included, particularly in relation to the main exposure of interest, this could lead to a biased estimate of the association for all Neovita enrolled infants.

It is worth considering how the exclusion of infants who died or who were lost to follow-up in the neonatal period might have influenced the effect estimates of the association between birth weight and BCG vaccination. **Table 6.1** summarises the characteristics of infants who exited the study in the neonatal period and who were excluded from the analysis, according to their vaccination status and birth weight.

Table 6.1: Vaccination status and birth weight of infants excluded from the analyses.

Vaccination status	**LBW N (% of total)**	**NLBW N (% of total)**	**Total N (% of total)**
Vaccination card seen, vaccinated, date known	21 (28)	54 (72)	76[1]
Vaccination card seen, known not vaccinated	32 (56)	25 (42)	57
Vaccination card seen, vaccinated, date unknown	37 (15)	206 (85)	243
Vaccination card not seen, known not vaccinated	0	0	0
Vaccination status unknown	125 (35)	235 (65)	362
Total	216 (29)	522 (71)	738

1. infant with unknown birthweight

A total of 738 infants were excluded from the BCG analysis, of whom 216 (29%) were LBW. Of these 738, 243 (33%) were vaccinated with an unknown date, and 362 (49%) had an unknown vaccination status. LBW infants made up a greater proportion of unvaccinated infants (56%) and infants whose vaccination status was unknown (35%). LBW infants comprised a smaller proportion of infants with unknown vaccination dates (15%).

LBW infants were more likely to be excluded from the analyses; however, since less than 2% of all enrolled infants with known vaccination status were excluded (76 vaccinated infants with a known date, 57 infants known not to be vaccinated, and 243 vaccinated infants with an unknown date), this is unlikely to have greatly affected the size of the effect estimates or the generalisability of the results.

Additional References for Chapter 6

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CHAPTER 7: USING ROUTINE HEALTHCARE CONTACTS TO IMPROVE THE VACCINATION OF LBW INFANTS

Preamble

The paper presented in this chapter addresses PhD objective 4, which is to investigate the potential for using routine contacts with health care providers to improve vaccine uptake, including among LBW infants, and to assess whether birth weight and other factors are determinants of uptake of opportunities. In ***Section 7.1****, I introduce the paper. I discuss the process for defining opportunities for vaccination (the main outcome for these analyses) in* ***Section 7.2*** *and* ***Section 7.3*** *presents the paper itself, including tables and graphs of results. The paper investigated a number of potential determinants of uptake, of which birth weight was one. However, as it did not otherwise specifically focus on LBW infants,* ***Section 7.4*** *presents an additional analysis that investigates how using opportunities could specifically improve the vaccination of LBW infants.* ***Section 7.4*** *includes a description of the methods for this analysis, and it presents and discusses the results of the analysis.*

7.1. INTRODUCTION

My aim for this paper was to investigate how contacts with the health service could be used to improve the vaccination of infants who were due but were not up to date with their vaccines. As discussed in **Chapter 1**, routine contacts with the health service could provide an easy and inexpensive way to improve vaccination for all infants, including LBW infants. However, in order for this to happen, vaccine and health care providers would need to pro-actively notice and address under-vaccination.

In this analysis, I investigated the extent to which health care providers did this in our study population, using four indicator vaccines, BCG, OPV3, DTP3 and measles. I investigated a) the frequency of opportunities for vaccination, b) the uptake of those opportunities for vaccination, and c) the impact that using those opportunities would have on vaccine uptake.

The outcomes for these analyses were 1) opportunities for vaccination (described in greater detail in **Section 7.2**, and in the paper itself), 2) determinants of uptake of opportunities (analysed using logistic regression) and 3) the proportions of infants who would have been vaccinated at specific time-points if their first opportunity was taken (2 and 3 described in greater detail in the paper). The study population for the analysis of frequency of opportunities was infants who were due vaccines, the study population for uptake and impact of using opportunities was infants who had opportunities. A more detailed description of the study populations for each analysis, including additional inclusion criteria is given in the paper.

7.2. DEFINING OPPORTUNITIES FOR VACCINATION

As described in **Chapters 2 and 3**, data were available on 1) reported care seeking for illness, 2) reported health facility admissions for illness (identified by dates of admission), and 3) visits for vaccination (identified by dates of vaccination).

I defined opportunities for vaccination as a contact with a health care provider for reasons other than to receive the vaccine of interest, for infants who were eligible but not up-to-date with their vaccines. I classified opportunities as 'primary-care based' (during a vaccination contact with a primary care provider in the community) and 'facility-based' (during a health facility admission). Reported care seeking visits were not included as opportunities, for the reasons discussed in point 3, below.

The process of defining opportunities for vaccination was complicated and reflected the complexity of the routine vaccination schedule in Ghana, as well as the numerous permutations in the actual order of vaccination in our study population. I, with the assistance of my supervisors, identified a number of criteria for exclusion from the above definition of opportunities:

1. The contact had to allow the administration of a valid vaccination dose in compliance with the recommended schedule. Contacts that occurred before the due date for vaccination were excluded. For OPV3 and DTP3, the contact had to be at least four weeks after the previously administered doses, as this is the minimum recommended gap between doses for these vaccines.

2. The contact had to be within the first year of life, as I was investigating opportunities within the first year of life.

3. It had to be possible to administer vaccines at the contact. All health facilities and child health clinics have the capacity to give vaccines. For reported care seeking, I did not have data on where care was sought. Care may have been sought from a variety of sources where there was no capacity to administer vaccines, such as traditional healers, pharmacists or drug sellers. For this reason, I excluded reports of care seeking for illness from my definition of opportunities, unless it was a documented health facility admission.

4. The contact should not have been specifically for the administration of the due vaccine. If a caretaker took a child to a child health clinic solely for the purpose of getting the due vaccine, then that could not be counted as an opportunity. The contact had to be for another reason to be counted as an opportunity. If I did not have evidence of this, the contact was excluded. The only data that allowed me to identify the contact as being associated with another activity was the administration of another unrelated (not co-scheduled) vaccine or a facility admission. If the contact was associated with the administration of a related / co-scheduled vaccine, it was excluded, for the reasons outlined below.

7.2.1. Exclusion of co-scheduled vaccines

As outlined in **Chapter 2**, the routine vaccination schedule in Ghana recommends the administration of OPV and DTP together at 6, 10 and 14 weeks of age, and the administration of measles and yellow fever together at 9 months of age. At the clinic both scheduled vaccines should automatically be given together. This analysis aimed to investigate the ability of health care providers to proactively identify and respond to instances of under-vaccination. Given this, I excluded from my definition of opportunities visits for a co-scheduled vaccine with which the vaccine of interest would have been given automatically (i.e. for DTP I excluded OPV vaccination visits, for OPV I excluded DTP vaccination visits, and for MCV vaccine I excluded yellow fever vaccination visits). If I had included these as opportunities, I would have risked overestimating the number of opportunities, and the uptake of opportunities. I discuss this further in **Section 7.4**.

7.3. PAPER 4: OPPORTUNITIES FOR INFANT VACCINATION IN GHANA, AND THE POTENTIAL IMPACT OF THEIR UTILISATION ON VACCINE UPTAKE.

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SECTION A – Student Details

Student	Maureen O'Leary
Principal Supervisor	Sara Thomas
Thesis Title	Low birth weight as a risk factor for undervaccination in rural Ghana; evidence from a population based cohort

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	American Journal of Tropical Medicine and Hygiene
Please list the paper's authors in the intended authorship order:	Maureen O'Leary, Sian Floyd, Karen Edmond, Sam Newton, Sara Thomas.
Stage of publication	Manuscript submitted

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I developed the idea for this research in collaboration with Sara Thomas and Sian Floyd. This research is based on a secondary analysis of data collected as part of a randomised control trial of neonatal vitamin A supplementation. I was the epidemiologist on the trial and I spent 3 years in Ghana overseeing and ensuring the quality of the data collected for the trial and subsequently included in this research. I cleaned the data and prepared the datasets used in the analyses. I developed the initial plan of analysis and revised this following detailed discussions with Sara Thomas and Sian Floyd, in particular relating to the choice of denominators used in the analyses, and on the definition of an opportunity for vaccination. Sian Floyd advised on the statistical methodology for the analyses. I wrote the program for the analyses, ran the analyses and drafted the manuscript. Sara Thomas and Karen Edmond provided advice on the interpretation of the results, and gave detailed comments on early drafts of the manuscript. All co-authors commented on the manuscript.

Student Signature:  **Date:** 27/7/16

Supervisor Signature:  **Date:** 27/7/16

Opportunities for infant vaccination in Ghana, and the potential impact of their utilisation on vaccine uptake.

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ABSTRACT

Background

We analysed how using healthcare contacts (opportunities) would improve vaccination in rural Ghana.

Methods

For each vaccine (Bacillus Calmette-Guerin (BCG), third dose oral polio vaccine (OPV3) and diphtheria-tetanus-pertussis (DTP3), and measles), we counted among eligible infants (known vaccination status, due vaccines), the number of opportunities (contacts for reasons other than receipt of the vaccine of interest) and their uptake (the proportion taken), stratified by type of opportunity: 'primary-care-based' (associated with getting an unrelated vaccine) and 'facility-based' (during an admission). Among those with opportunities, we i) calculated adjusted odds ratios (aOR) of the determinants of primary-care-based opportunity uptake using logistic regression, and ii) calculated how using the first opportunity would improve vaccination at 4, 8 and 12 weeks after the due date.

Results

Of eligible infants, 50.8% (2591/5105) for BCG, 6.7% (1451/21581) for OPV3, 4.8% (1046/21689) for DTP3, and 14.8% (3067/20726) for measles needed opportunities. Of those needing opportunities, 95.9% (2485/2591) had opportunities for BCG, 38.2% (554/1451) for OPV3, 22.2% (232/1046) for DTP3, and 22.3% (685/3067) for measles. Most BCG opportunities (94%, 3358) were associated with, and uptake was highest (54%, 1806/3358) when the infant received DTP/OPV vaccines at 6-14 weeks. Uptake was lower for measles/yellow fever contacts at 9 months onwards (10%, 12/125) and facility-based contacts (1%, 1/71). Compared to infants who were vaccinated before age 8 weeks, uptake of BCG opportunities was 85% less likely (aOR=0.14; 95%CI:0.10-0.19) 24 weeks or more after the BCG due date. For BCG, exploiting the first opportunity would have appreciably improved uptake at 4 (from 47% to 61%), 8 (from 74% to 91%) and 12 (from 83% to 97%) weeks after the due date.

Conclusions
Routine healthcare contacts are under-utilised to vaccinate those under-served by vaccination in Ghana, especially contacts occurring 6 months after the due date and those associated with admissions.

Keywords: routine childhood vaccination, missed opportunities, Ghana, epidemiology

INTRODUCTION

Currently one in five children does not receive the full schedule of vaccines as recommended by the Expanded Programme on Immunisation), and many are vaccinated late[1,2]. The Global Vaccine Action Plan (2011-2020)[1] stresses that each contact with a healthcare provider should be used to verify vaccination status and to vaccinate when indicated[1]. The World Health Organisation (WHO) also recommends that the vaccination status of children admitted to health facilities be assessed, and due vaccines administered prior to discharge.[3]

We aimed to evaluate how exploiting routine contacts with healthcare providers could improve vaccination, by analysing data from a large randomised controlled trial undertaken in Ghana between October 2010 and February 2013. This trial collected high-quality data on vaccination and specific contacts with healthcare providers at monthly intervals for the first year of life. The Ghanaian routine vaccination programme recommends the administration of Bacillus Calmette-Guerin (BCG) and oral polio vaccine (OPV) at birth, OPV and the pentavalent diphtheria, tetanus, pertussis, haemophilus influenza B, and hepatitis B vaccine (DTP/HiB/HepB hereafter known as DTP) at 6, 10 and 14 weeks of age, and measles containing vaccine (MCV) and yellow fever (YF) at nine months of age. As the potential to improve vaccine delivery through exploiting routine healthcare contacts may vary depending on the type of vaccine and the recommended age of administration, our analyses focused on BCG, third dose OPV (OPV3) and DTP (DTP3), and MCV.

Our objectives were, for each of these vaccines to 1) quantify among infants' due vaccination, the frequency and uptake of opportunities for vaccination in the first year of life, and to assess among infants with opportunities 2) the determinants of opportunity uptake, and 3) how using the first opportunity could increase vaccine uptake.

METHODS

The Neovita trial, conducted at the Kintampo Health Research Centre (KHRC) in Ghana, evaluated the impact of neonatal vitamin A supplementation on infant mortality[4]. We have recounted the trial procedures elsewhere[4,5]. Trained field staff collected data on infant and maternal factors at baseline, and of vaccination and health facility admissions at monthly follow-up visits for the first year of life. Data on vaccinations, administered at birth in health facilities or given subsequently at child health clinics, Community Health Planning System (CHPS) compounds or mobile vaccination clinics, were extracted from the infant's written vaccination record, and supplemented by maternal recall (≤1% of all data). Data on admissions, including admission and discharge dates, were based on maternal report.

The study population for the first objective (quantifying the number of opportunities) were infants in follow-up, due vaccination, with known vaccination status and dates. Infants with complete covariate data with vaccination opportunities were included in the analysis of the second objective (determinants of opportunity uptake). Those with opportunities were the study population for the third objective (impact of using the first opportunity).

Definitions

We defined infants as: 1) vaccinated (known date) when they had a plausible vaccination date on their written record; 2) vaccinated (unknown date) when they had an illegible or implausible date on their record; 3) unvaccinated when they consistently had no evidence of vaccination on their record and no documented date, or when their record was never viewed and their mothers consistently reported them as unvaccinated; 4) vaccination status unknown if their record was never viewed and their mother reported them as vaccinated without specifying the vaccine, or there was no information on whether they were vaccinated as they were never seen in follow-up.

Among eligible infants due a specific vaccine, we defined opportunities as contacts with a healthcare provider for reasons other than to receive the vaccine of interest. We classified opportunities as 'primary-care-based' (during a contact with a primary-care provider to receive an unrelated vaccine) and 'facility-based' (during a facility admission).

As our interest was in capturing healthcare workers' ability to take advantage of an unrelated contact to administer a due vaccine, we excluded contacts in which a due vaccine was given on its own without another vaccine or admission, as mothers may have brought their infants to the health centre solely to get the vaccine. Similarly, we excluded visits for a co-scheduled vaccine with which the vaccine of interest would have been given

automatically (for DTP3 we excluded OPV vaccination visits, for OPV we excluded DTP vaccination visits, and for MCV vaccine we excluded yellow fever vaccination visits).

Facility-based opportunities were classified as 'taken' if the due vaccine was given between the admission and discharge dates.

We followed the approach of Clark and Sanderson[2], Hutchins et al[6], and Kahn et al[7], and counted opportunities from the vaccine due date. For BCG the due date was any time up to the end of the neonatal period (4 weeks/28 days of age)[8]. Follow-up ended at age one year, at exit from the study, or when the infant received the vaccine of interest, depending on which came first.

All analyses were conducted using STATA 14.1 (STATACORP, 2015).

For each vaccine (BCG, OPV3, DTP3 and MCV), we counted the number of opportunities and calculated the opportunity uptake rate as the proportion of these opportunities that were 'taken', stratified by type of opportunity (primary-care-based and facility-based).

We used multivariable logistic regression to calculate adjusted odds ratios (aOR) of the determinants of opportunity uptake. Model construction was informed by a hierarchical framework[9] of the determinants of vaccination, starting with an initial model of distal determinants (for example socioeconomic status), then adding the proximal determinants (like birth weight), and finally adjusting for neonatal infant illness (as a possible mediator of uptake of opportunities[10]). We used robust standard errors to account for clustering associated with infants who had more than one opportunity during follow-up.

For each vaccine we generated Kaplan-Meier curves of the actual times to vaccination (using the actual date of vaccination) and the theoretical times to vaccination (if the first vaccination opportunity was taken). To assess how exploiting opportunities would improve uptake over time, we calculated actual and theoretical uptake rates at 4, 8, and 12 weeks after the vaccine due date, and at 52 weeks of age for all vaccines.

The Ethics Committees of the World Health Organisation (WHO), the London School of Hygiene & Tropical Medicine (LSHTM) and the KHRC approved the conduct of the trial.

The Neovita trial was funded by the Bill and Melinda Gates Foundation.

RESULTS

Of 22,955 Neovita enrolled infants, the numbers eligible for inclusion in the analyses of frequency and uptake of opportunities for each vaccine (infants with known vaccination status and dates who were in follow-up and who were due vaccination) were a) 5105 (22%) for BCG, b) 21581 (94%) for OPV3, c) 21689 (95%) for DTP3 and 20726 infants (90%) for MCV (**Table 1**). Most of these infants were vaccinated at a scheduled visit or were given the vaccine on its own before any unrelated healthcare contact (**Table 1**). Consequently, those needing opportunities were, except for BCG, small. For BCG 50.8% (2591/5105) of eligible infants needed opportunities, compared to 6.7% (1451/21581) for OPV3, 4.8% (1046/21689) for DTP3, and 14.8% (3067/20726) for MCV. Of 2591 infants needing BCG opportunities, 2485 (95.9%) had opportunities, compared to 38.2% (554/1451) of those needing OPV3 opportunities, 22.2% (232/1046) of those needing DTP3 opportunities, and 22.3% (685/3067) of those needing MCV opportunities (**Table 1**).

Infants had a median of one, and a maximum of seven opportunities for BCG vaccination (**Web Figure 1**). Most BCG opportunities (98%, 3483) were primary-care-based, and almost all (94%, 3358) were associated with OPV/DTP vaccination (scheduled at age 6-14 weeks). BCG opportunity uptake was highest (54%, 1806/3358) for these earlier OPV/DTP related opportunities, and lower for MCV/YF related opportunities (10%, 12/125) (scheduled at 9 months) or facility-based opportunities (1%, 1/71) (**Table 1**). Uptake was highest (62.7%) for the first primary-care-based opportunity, and declined thereafter (33.4% for the second, 22.4% for the third, 12.3% for the fourth, and zero for the fifth, sixth and seventh) (**Web Figure 1**).

There were fewer opportunities for OPV3, DTP3 and MCV vaccination, and a lower proportion of these were primary-care-based (63% (394/622) for OPV3, 28% (65/232) for DTP3 and 26% (193/736) for MCV). For each of these vaccines, fewer than 10% of all opportunities were taken (**Table 1**). Uptake of opportunities for vaccines other than BCG was low, regardless of whether it was the first, second or subsequent opportunity (**Web figures 2, 3 and 4**).

Due to small numbers of primary-care-based and facility-based opportunities and the small number of taken opportunities for OPV3, DTP3 and MCV vaccination (**Table 1, Web figures 1-4**), the analysis of determinants of uptake of opportunities was restricted to BCG primary-care-based opportunities.

Compared to all Neovita enrolled infants, (**Table 2**), the 5105 infants who were BCG unvaccinated and in follow up at the end of the neonatal period were more likely to be poorer, to be farmers, with lower educational attainment, living further from a health facility, and not born in a health facility. Among those 5105, there was little difference between the 2439 included in the analyses, compared to those excluded (because they had no opportunities (n=2620) or they were missing covariate data (n=46)) (**Table 2**).

There was a marked linear decline in the likelihood of opportunity uptake over time, with lower uptake the further away the opportunities were from the BCG due date (p-trend<0.0001) (**Table 3**), having adjusted for all other explanatory variables. Compared to those within eight weeks of the due date, uptake was 30% less likely (aOR=0.70; 95%CI:0.59-0.83) for opportunities 9-12 weeks after the due date, almost 70% less likely (aOR=0.31; 95%CI:0.26-0.38) for opportunities 13-24 weeks after the due date, and >85% less likely (aOR=0.14; 95%CI:0.10-0.19) for opportunities >24 weeks after the due date.

There was some evidence of an association with maternal occupation, with increased uptake of BCG opportunities for infants whose mothers were self-employed (aOR=1.46; 95%CI:1.17-1.80), compared to farmers, even after adjusting for more proximal variables. No other factor was observed to have an effect on the uptake of BCG vaccine-provider opportunities, nor was infant illness found to have a mediating effect (**Table 3**).

Among those with opportunities, exploiting the first opportunity would have increased uptake considerably in the 4, 8 and 12 weeks after the due date for each vaccine (**Figure 1, Table 4**).

For BCG vaccine uptake would have increased from 46.6% (95%CI:44.7-48.6) to 61.1% (95%CI:59.2-63.0) at 4 weeks after the due date, from 73.8% (95%CI:72.0-75.5) to 90.8% (95%CI:89.7-92.0) by 8 weeks after the due date, and from 83.1% (95%CI:81.6-84.6) to 97.2% (95%CI:96.6-97.9) by 12 weeks after the due date (**Table 4**). For OPV3, vaccine uptake would have more than doubled at 4 weeks after the due date, from an actual uptake of 7.8% (95%CI:5.9-9.7) to 19.5% (95%CI:16.7-22.3), and would have almost doubled again by 8 weeks, from 18.7% (95%CI:15.9-21.4) to 31.6% (95%CI:28.4-34.9). By 12 weeks, uptake would have increased from 39.9% (95%CI:36.5-43.4) to 45.7% (95%CI:42.1-49.2) (**Table 4**). Similar substantive improvements in uptake of DTP3 and MCV would have occurred (**Table 4)**.

DISCUSSION

This study investigated the potential for using health service contacts to improve vaccine uptake for infants under-served by vaccination in Ghana. For most vaccines except BCG, the percentage of under-served infants who needed opportunities was comparatively small (50.8% of eligible infants for BCG, 6.7% for OPV3, 4.8% for DTP3, and 14.8% for MCV), however under-served infants are more likely to come from marginalised populations where the burden of disease is highest, and where vaccination may have the greatest impact. Ensuring their vaccination is essential to fulfil global disease eradication and elimination goals[1].

Where opportunities existed, in many cases these were missed by vaccine providers and other healthcare providers. Although for BCG, the uptake of primary care opportunities was >50%, for other vaccines uptake of these opportunities was <10%, suggesting a failure to systematically assess the overall vaccination status of infants attending for routine vaccination and to administer due vaccines. Similarly, facility-based opportunities were largely unexploited with opportunity uptake of <10% for all vaccines. This suggests a lack of compliance with recommendations to assess and vaccinate infants prior to discharge[3], and a fragmentation of curative care and vaccination services in our study area. Facility-based opportunities were particularly important for vaccines scheduled later in the programme, as they were for many infants the only opportunities for vaccination.

For BCG vaccination, vaccine-providers were less likely to administer BCG, the further away the opportunity was from the due date. Vaccine-providers may forget about administering overdue BCG when they are giving later scheduled vaccines such as measles.

For those having opportunities, we showed that substantive improvements to uptake could be achieved. It is evident from the characteristics of infants with BCG opportunities (born to poorer mothers with lower levels of education and occupational grade, living further from health facilities and who delivered at home), that ensuring the utilisation of all opportunities to vaccinate would help in tackling the known inequities[11] in vaccine service delivery in our study population[11]. It is notable however that, for MCV, a large proportion of infants who needed opportunities had no known opportunities for vaccination in the three months between the due date and the end of follow-up, so even if all contacts were exploited, a core group would remain unvaccinated at the end of infancy. In the first year of life, infants in Ghana have only one scheduled vaccination visit after OPV3/DTP3

vaccination and none after MCV. For MCV, primary-care-based opportunities were frequently due to the late administration of BCG, OPV and DTP vaccines.

Some studies[7,12,13] have counted every contact with a healthcare provider as an opportunity for vaccination, even those where the infant was specifically being brought for the vaccine of interest. We followed the approach of Clark and Sanderson[2], and only included contacts for reasons other than receipt of the vaccine of interest. Consequently, our definition excluded opportunities associated with the administration of co-scheduled vaccines such as OPV opportunities for DTP vaccination and vice versa, as we assumed that the vaccine would be given automatically and not because the vaccine-provider recognised the need to administer a due dose.

We present minimum estimates of the number of opportunities for vaccination in our study area. For instance, we excluded vaccines due and given alone without any other vaccine or associated admission, as we didn't know if the contact was intended for a reason other than the administration of that particular vaccine. Regarding contacts associated with illness, reported care seeking contacts with healthcare providers that did not result in an admission were not counted, as we lacked information on the nature of these contacts and whether they could have been used for vaccination. It is likely that the number of opportunities for vaccination and their potential to improve vaccination in our study area is even greater than our estimates indicate.

Few studies have investigated vaccination opportunities in Africa, and most available data[6,7,13] are more than 20 years old. More recently, it has been reported that 26% of infants in Mozambique had at least one missed vaccination opportunity[12], substantively higher than in our study. This difference may reflect a) our more cautious approach to defining opportunities as described above, as well as b) lower vaccine uptake rates in the Mozambique study area (<75% for all vaccines) compared to our study area. Regarding opportunity uptake, the analysis of DHS data collected from 1996- 2005 in 24 African countries reported that, among those with opportunities, 17% to 71% of opportunities for DTP3 and MCV vaccination were taken (mean=41%)[2]. Higher uptake rates for primary-care-based opportunities compared to facility-based opportunities have previously been reported[7]. As suggested by our findings, failure to administer vaccines simultaneously, and a lack of assessment of vaccination status have previously been reported as determinants of uptake of opportunities[6]. Additional reported factors, for which we lacked data, include false contraindications to vaccination, fear of wasting vaccine by opening a vial for a small

number of children (particularly for BCG vaccination), vaccine shortage, poor organisation of vaccine clinics, and a lack of a daily vaccination clinic[6].

Strengths and Limitations

Our study benefited from low loss to follow-up rates (<3%), from the fact that the sample was population-based, and from the high-quality of the vaccination data. Vaccination data were collected at monthly intervals, using both written record and maternal recall, and we employed a rigorous approach to identifying and resolving inconsistencies in these data. Similarly, data on admissions, which were based on maternal recall, were collected on a monthly basis, thus minimising the potential for under-reporting and misclassification of these data.

Our study was also subject to a number of potential limitations. Due to small numbers we were unable to investigate the determinants of uptake of facility-based opportunities or primary-care-based opportunities for vaccines other than BCG, and so we were unable to assess whether their determinants differed to those of BCG opportunity uptake. We included nine explanatory variables in our final multivariable model, thus increasing the risk of finding an association due to chance due to multiple testing. However, the strong evidence of a graded effect with increasing time since the vaccine due date ($p<0.001$) seems unlikely to be due to a Type 1 error. Finally, the main trial did not collect qualitative data on either maternal, vaccine-providers' or healthcare providers' reasons for not utilising vaccination opportunities, which limits our ability to fully understand the drivers of missed vaccination opportunities. Nonetheless, our analyses provide clear evidence that failure to co-administer vaccines and poor integration between vaccination and curative care services are major contributors to missed opportunities in our study population.

Since undertaking this study, vaccines against pneumococcus and rotavirus, and a second MCV dose have been added to the national childhood vaccination schedule in Ghana. As the complexity of the vaccination programme and the number of antigens to be given together increases, the importance of exploiting all vaccination opportunities will also increase to ensure that children are fully vaccinated.

CONCLUSIONS

Our study highlights the unexploited potential for using routine healthcare contacts to vaccinate those under-served by vaccination in Ghana; doing so may help to address some of the persisting inequities in vaccine uptake. This could be easily achieved through simple

changes to vaccine service delivery, such as assessing all infants who attend vaccination clinics to see if they are fully vaccinated and vaccinating them if they are not. Vaccine providers should be educated to do this. Greater integration of vaccination services with curative care is needed. Further research on the reasons for missed opportunities should be undertaken to address other possible reasons for missing opportunities, such as poor scheduling and organisation of clinics, fear of wastage and other false contraindications[6].

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TABLES AND FIGURES

Table 1: Opportunities and uptake of opportunities for vaccination

a) Infants included & their opportunities for vaccination

		Number (%) of infants			
				Needed Opportunities	
Vaccine	Eligible[1] N (%)	Vaccinated at scheduled visit	Vaccinated alone	No opportunities, not vaccinated	Had opportunities
BCG	5105 (22.2)	-	2514 (49.2)	106 (2.1)	2485 (48.7)
OPV3	21581 (94.0)	19902 (92.2)	228 (1.1)	897 (4.2)	554 (2.6)
DTP3	21689 (94.5)	19961 (92.0)	682 (3.4)	814 (3.8)	232 (1.1)
Measles	20726 (90.3)	17414 (84.0)	245 (1.4)	2382 (11.5)	685 (3.3)

b) Count and uptake of opportunities by i) type of opportunity, and ii) associated vaccine.

	i) Type of Opportunity					ii) Associated vaccine[2]					
Vaccine		Facility-based		Primary-care based		BCG		MCV/YF		Any OPV/DTP	
	Total	N (% of total)	Uptake (%)	N (% of total)	Uptake (%)	Total	Uptake (%)	Total	Uptake (%)	Total	Uptake (%)
BCG	3554	71 (2.0)	1 (1.4)	3483 (98.0)	1818 (52.2)	-	-	125	12 (9.6)	3358	1806 (53.8)
OPV3	622	228 (36.7)	21 (9.2)	394 (63.3)	6 (1.5)	7	1 (14.3)	387	5 (1.3)	-	-
DTP3	232	188 (81.0)	8 (4.3)	65 (28.0)	5 (7.7)	4	1 (25.0)	61	4 (6.6)	-	-
Measles	736	543 (73.8)	43 (8.4)	193 (26.2)	6 (3.1)	9	0 (0.0)	-	-	184	6 (3.3)

1. In follow-up & unvaccinated at due date 2) For primary-care- based opportunities, opportunities were associated with the delivery of other vaccines. For instance, for BCG opportunities, MCV/YF associated vaccines indicates that the BCG opportunity was associated with the delivery of MCV/YF vaccines.

Table 2: Baseline characteristics of infants included in the analyses of determinants of uptake of BCG primary care based opportunities.

		5105 eligible[1]	
Variable	All Enrolled Infants Total = 22955	Excluded (No Opportunities (n=2620) or missing covariate data) (n=46) Total = 2666	Included (Had Opportunities) Total = 2439[2]
Ethnicity/Religion			
Akan	10693 (46.6)	994 (37.3)	897 (36.8)
Non-Akan/Non-Christian	5879 (25.6)	765 (28.7)	754 (30.9)
Non-Akan/Christian	6383 (27.8)	907 (34.0)	788 (32.3)
Socioeconomic status			
1 (poorest)	4510 (19.7)	866 (32.5)	760 (31.2)
2	4550 (19.8)	658 (24.7)	617 (25.3)
3	4583 (20.0)	560 (21.0)	463 (18.9)
4 (richest)	9312 (40.6)	582 (21.8)	599 (24.5)
Occupation			
Gov/Private/Self-employed/Other	10171 (44.3)	824 (30.9)	837 (33.3)
Farming	6671 (29.1)	1149 (43.1)	943 (38.6)
Does not work	6113 (26.6)	693 (26.1)	659 (27.0)
Maternal education			
None	7127 (31.1)	1080 (40.5)	964 (39.5)
Primary school	4236 (18.5)	552 (20.7)	505 (20.7)
Secondary / tertiary	11578 (50.5)	1031 (38.7)	970 (39.8)
Missing	14	3 (0.1)	
Sex			
Male	11649 (50.8)	1421 (53.3)	1291 (53.0)
Female	11306 (49.3)	1245 (46.7)	1148 (47.0)
Age/Parity			
<20	2645 (11.5)	337 (12.6)	314 (12.9)
20-29, 1-3 kids	8078 (35.2)	849 (31.8)	753 (30.9)
20-29, 4 or more kids	3963 (17.3)	530 (19.9)	478 (19.6)
>=30, 1-3 kids	1137 (5.0)	90 (3.4)	84 (3.4)
>=30, 4 or more kids	7102 (30.9)	848 (31.8)	810 (33.2)
Missing	30	12 (0.5)	
Distance			
<1.00km	13880 (60.5)	1379 (51.7)	1197 (49.1)
1.00-4.99km	5285 (23.0)	617 (23.1)	532 (21.8)
>=5.00km	3787 (16.5)	669 (25.1)	710 (29.1)
Missing	3	1 (0.1)	
Place of birth			
Facility	17581 (76.6)	1636 (61.4)	1451 (59.5)
Non-facility	5374 (23.4)	1030 (38.7)	988 (40.5)
Birth weight			
>=2.5kg	19361 (84.4)	2167 (81.3)	2052 (84.1)
2.00-2.49kg	3031 (13.2)	417 (15.6)	321 (13.2)
1.50-1.99kg	444 (1.9)	64 (2.4)	52 (2.1)
<1.50kg	117 (0.5)	18 (0.7)	14 (0.6)
Missing	2		

1. Unvaccinated & in follow-up at the end of the neonatal period
2. *Excludes 46 infants with opportunities who were missing covariate data*

Table 3: Determinants of uptake of postneonatal BCG primary care based opportunities (n=3438)

	Vaccinated / Total	Proportion of opportunities taken (95%CI)	Unadjusted odds ratio OR (95%CI) (p-value)	Adjusted for distal determinants aOR (95%CI) (p-value)	Adjusted for distal & proximal determinants (final model) aOR (95%CI) (p-value)	Final model adjusted for mediating effects of infant illness aOR (95%CI) (p-value)
Ethnicity/Religion						
Akan	647/1201	53.9 (51.1-56.7)	Ref	Ref	Ref	Ref
Non-Akan/non-Christian	579/1084	53.4 (50.4-56.4)	0.98 (0.80-1.21)	1.10 (0.86-1.41)	1.13 (0.90-1.42)	1.13 (0.90-1.43)
Non-Akan/Christian	565/1153	49.0 (46.1-51.9)	0.82 (0.67-1.00)	0.94 (0.75-1.17)	0.94 (0.76-1.15)	0.94 (0.76-1.16)
			(p=0.1066)	(p=0.3370)	(p=0.1881)	(p=0.1868)
Socioeconomic status						
1 (poorest)	565/1144	49.4 (46.5-52.3)	Ref	Ref	Ref	Ref
2	454/891	51.0 (47.7-54.2)	1.06 (0.86-1.32)	0.99 (0.79-1.23)	0.92 (0.75-1.14)	0.93 (0.75-1.14)
3	329/638	51.6 (47.7-55.4)	1.09 (0.86-1.39)	0.95 (0.73-1.24)	0.88 (0.69-1.13)	0.90 (0.70-1.15)
4 (richest)	433/765	57.9 (54.4-61.4)	1.41 (1.12-1.78)	1.11 (0.85-1.46)	0.97 (0.74-1.28)	0.99 (0.76-1.30)
			(p=0.0322)	(p=0.7156)	(p=0.7175)	(p=0.7446)
Maternal occupation						
Gov/Priv/Other/ Self-employed	633/1078	58.7 (55.8-61.7)	1.59 (1.30-1.94)	1.47 (1.17-1.85)	1.46 (1.17-1.80)	1.46 (1.17-1.80)
Farming	675/1428	47.3 (44.7-49.9)	Ref	Ref	Ref	Ref
Does not work	483/932	51.8 (48.6-55.0)	1.20 (0.98-1.47)	1.14 (0.91-1.41)	1.23 (0.98-1.55)	1.23 (0.98-1.55)
			(p<0.0001)	(p=0.0033)	(p=0.0029)	(p=0.0029)
Maternal education						
None	715/1424	50.2 (47.6-52.8)	0.83 (0.69-1.01)	0.92 (0.72-1.17)	0.97 (0.78-1.22)	0.98 (0.78-1.23)
Primary school	370/725	51.0 (47.4-54.7)	0.86 (0.69-1.07)	0.94 (0.74-1.18)	1.01 (0.81-1.26)	1.02 (0.82-1.27)
Secondary / tertiary	706/1289	54.8 (52.1-57.5)	Ref	Ref	Ref	Ref
			(p=0.1492)	(p=0.7708)	(p=0.9411)	(p=0.9456)
Sex						
Male	960/1772	54.2 (51.9-56.5)	Ref	Ref	Ref	Ref
Female	831/1666	49.9 (47.5-52.3)	0.84 (0.71-0.99)	0.85 (0.72-1.01)	0.90 (0.77-1.05)	0.90 (0.77-1.05)
			(p=0.0433)	(p=0.0601)	(p=0.1776)	(p=0.1702)

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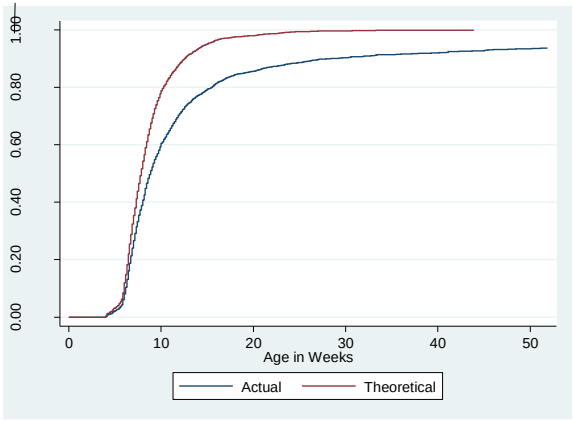
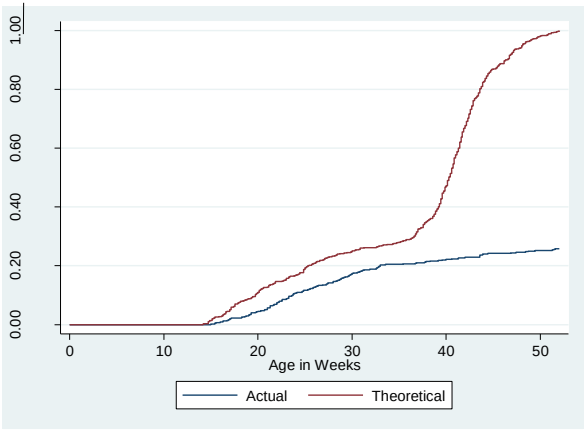
	Vaccinated / Total	Proportion of opportunities taken (95%CI)	Unadjusted odds ratio OR (95%CI) (p-value)	Adjusted for distal determinants aOR (95%CI) (p-value)	Adjusted for distal & proximal determinants (final model) aOR (95%CI) (p-value)	Final model adjusted for mediating effects of infant illness aOR (95%CI) (p-value)
Age/Parity						
<20	223/449	49.7 (45.0-54.3)	Ref		Ref	Ref
20-29, 1-3 kids	565/1052	53.7 (50.7-56.7)	1.18 (0.89-1.55)		1.08 (0.82-1.42)	1.08 (0.82-1.43)
20-29, 4 or more kids	351/718	48.9 (45.2-52.5)	0.97 (0.72-1.31)		1.05 (0.78-1.42)	1.06 (0.78-1.42)
>=30	652/1219	0.53 (0.51-0.56)	1.17 (0.94-1.45)		1.17 (0.87-1.57)	1.18 (0.88-1.58)
			(p=0.0590)		(p=0.6714	(p=0.6409)
Distance to health facility						
<1.00km	899/1621	55.5 (53.0-57.9)	Ref		Ref	Ref
1.00-4.99km	357/714	50.0 (46.3-53.7)	0.80 (0.65-1.00)		0.81 (0.66-0.99)	0.81 (0.66-0.99)
>=5.00km	535/1103	48.5 (45.6-51.5)	0.76 (0.62-0.92)		0.95 (0.78-1.15)	0.95 (0.78-1.15)
			(p=0.0105)		(p=0.1233)	(p=0.1201)
Place of birth						
Facility	1070/1983	54.0 (51.8-56.2)	Ref		Ref	Ref
Non-facility	721/1455	49.6 (47.0-52.1)	0.84 (0.71-0.99)		0.99 (0.83-1.18)	0.99 (0.83-1.18)
			(p=0.0405)		(p=0.9165)	(p=0.8986)
Birth weight						
>=2.5kg	1518/2883	52.7 (50.8-54.5)	Ref		Ref	Ref
<2.50kg	273/555	49.2 (45.0-53.4)	0.87 (0.69-1.10)		0.97 (0.78-1.20)	0.97 (0.78-1.20)
			(p=0.2390)		(p=0.7672)	(p=0.7875)
Timing of opportunity						
5-8 weeks post due date	867/1324	65.5 (62.9-68.0)	Ref		Ref	Ref
9-12 week post due date	550/967	56.9 (53.8-60.0)	0.70 (0.59-0.82)		0.70 (0.59-0.83)	0.70 (0.59-0.82)
13-24 weeks post due date	320/879	36.4 (33.2-39.6)	0.30 (0.25-0.36)		0.31 (0.26-0.38)	0.31 (0.26-0.38)
25-52 weeks post due date	54/268	20.1 (15.3-25.0)	0.13 (0.10-0.18)		0.14 (0.10-0.19)	0.14 (0.10-0.19)
			(p<0.0001)		(p<0.0001)	(p<0.0001)
Illness						
No	1563/2979	52.5 (50.7-54.3)	Ref			Ref
Yes	228/459	49.7 (45.1-54.3)	0.89 (0.73-1.09)			0.62 (0.31-1.23)
			(p=0.2745)			(p=0.1710)

Figure 1: Probability of A) BCG B) OPV3, C) DTP3, and D) MCV vaccination in the first year of life associated with the actual vaccination date and the theoretical vaccination date associated with exploiting the first opportunity for vaccination.

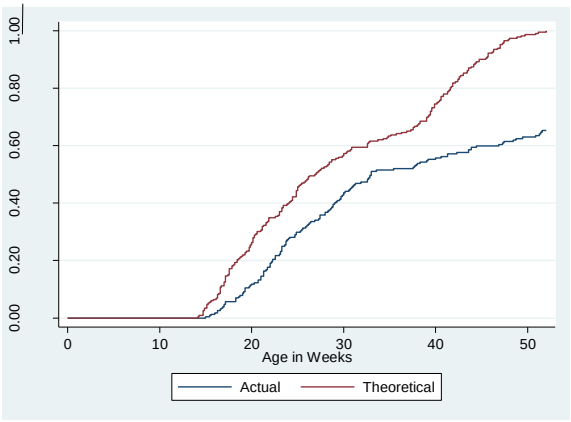
A.



B.



C.



D.

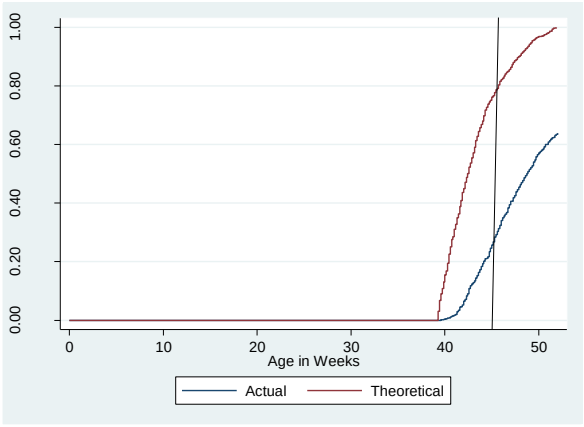


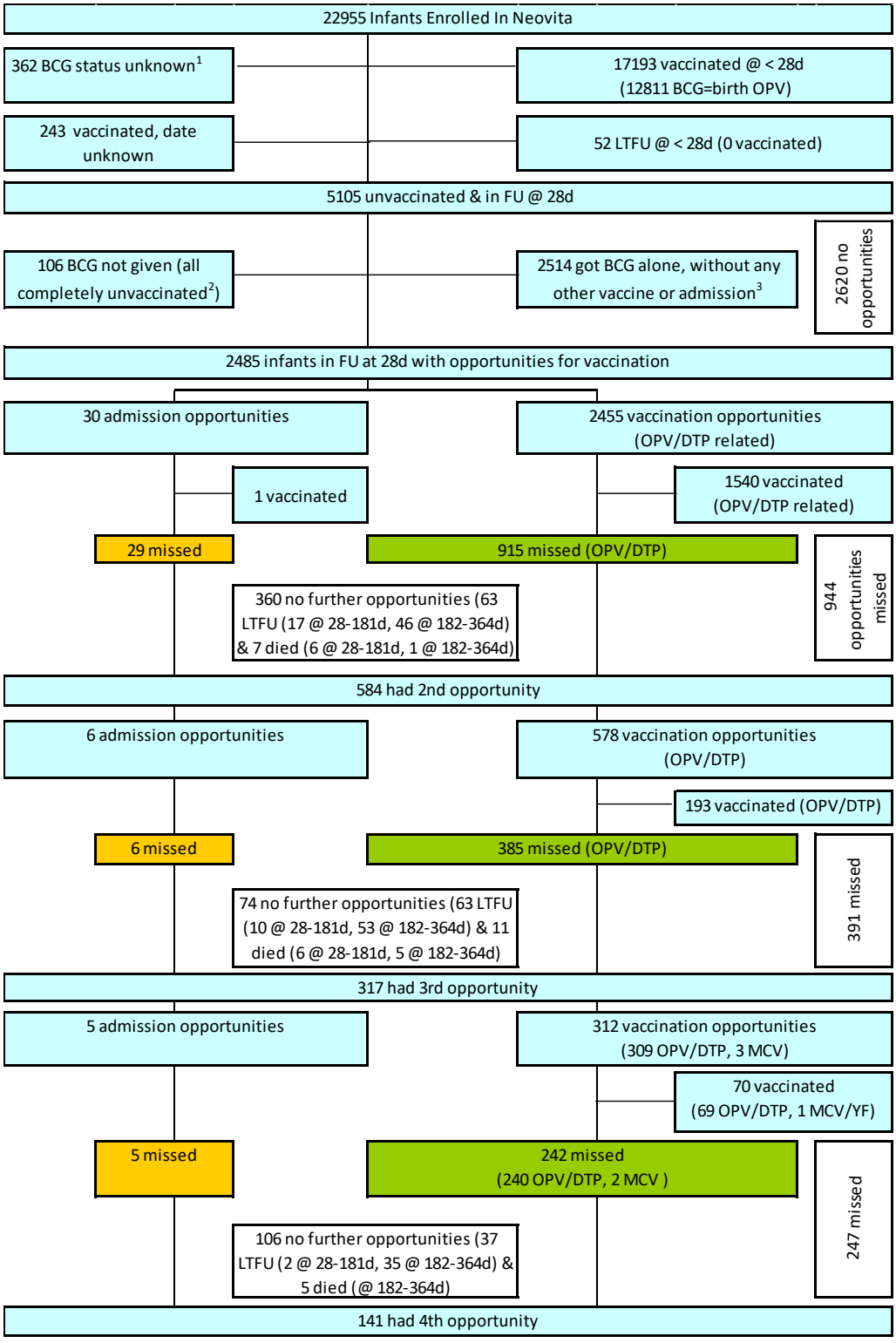
Table 4: Uptake rates at selected time-points associated with actual vaccination dates and with utilising the first opportunity for vaccination

	Uptake Rate (95%CI)							
	Due date + 4 weeks		Due date + 8 weeks		Due date + 12 weeks		52 weeks of age	
Vaccine	**Actual**	**Theoretical**	**Actual**	**Theoretical**	**Actual**	**Theoretical**	**Actual**	**Theoretical**
BCG*	46.6	61.1	73.8	90.8	83.1	97.2	93.1	100.0
	(44.7-48.6)	(59.2-63.0)	72.0-75.5)	(89.7-92.0)	(81.6-84.6)	(96.6-97.9)	(92.1-94.1)	(100.0-100.0)
OPV3	7.8	19.5	18.7	31.6	28.1	39.9	45.7	100.0
	(5.9-9.7)	(16.7-22.3)	(15.9-21.4)	(28.4-34.9)	(25.0-31.3)	(36.5-43.4)	(42.1-49.2)	(100.0-100.0)
DTP3	25.7	40.3	44.5	61.3	60.0	73.9	83.5	100.0
	(22.1-29.3)	(36.3-44.4)	(40.4-48.6)	(57.2-65.3)	(56.0-64.1)	(70.3-77.6)	(80.4-86.5)	(100.0-100.0)
Measles	0.4	14.6	22.1	73.7	54.6	94.9	75.8	100.0
	(0.0-0.9)	(11.5-17.6)	(18.6-25.7)	(70.0-77.5)	(50.4-58.9)	(93.0-96.8)	(72.1-79.5)	(100.0-100.0)

* uptake rates are calculated at 4, 8 and 12 weeks after the end of the neonatal period (age 4 weeks)

Web Appendix

Web figure 1: Opportunities and uptake of opportunities for BCG vaccination



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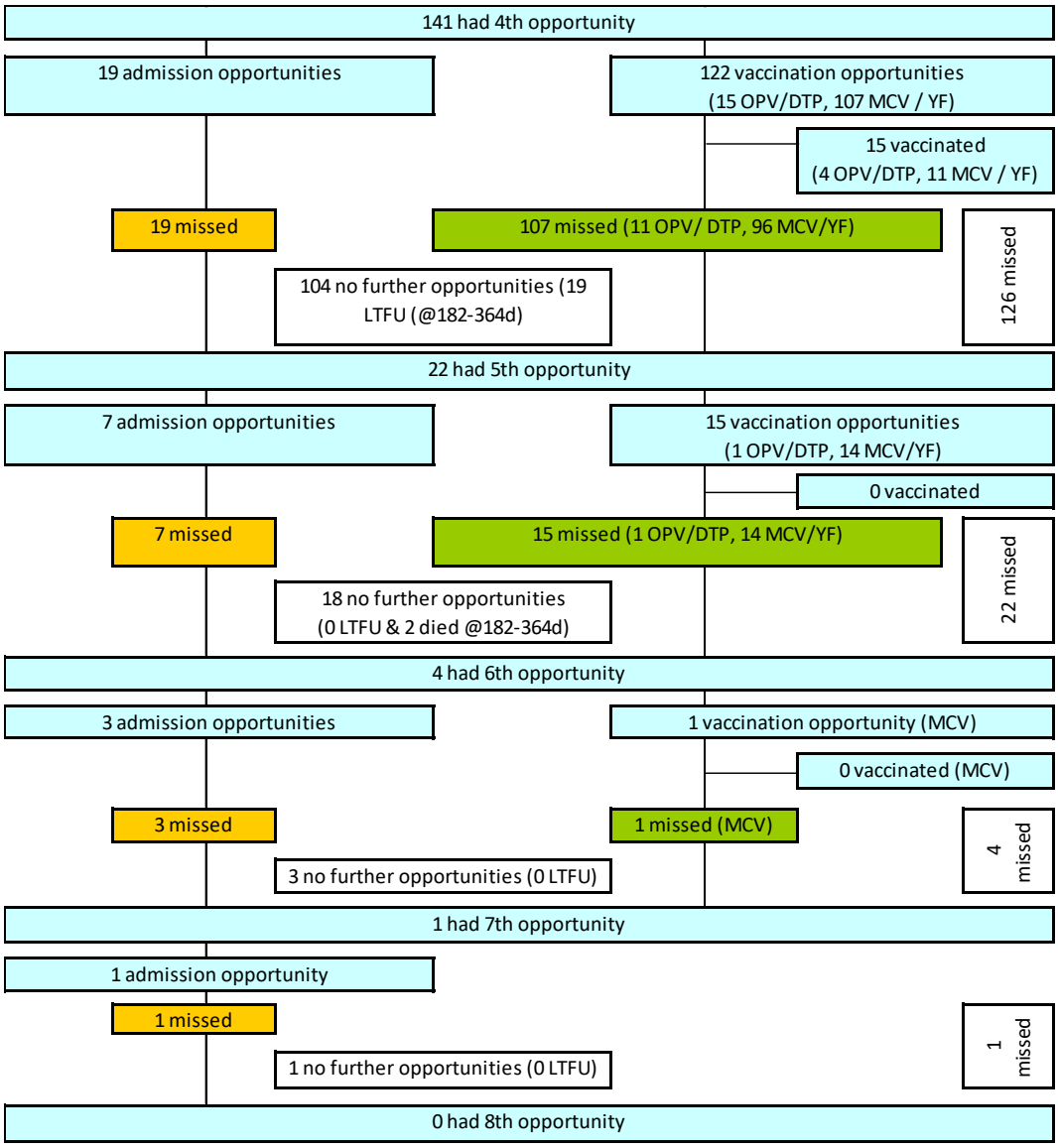
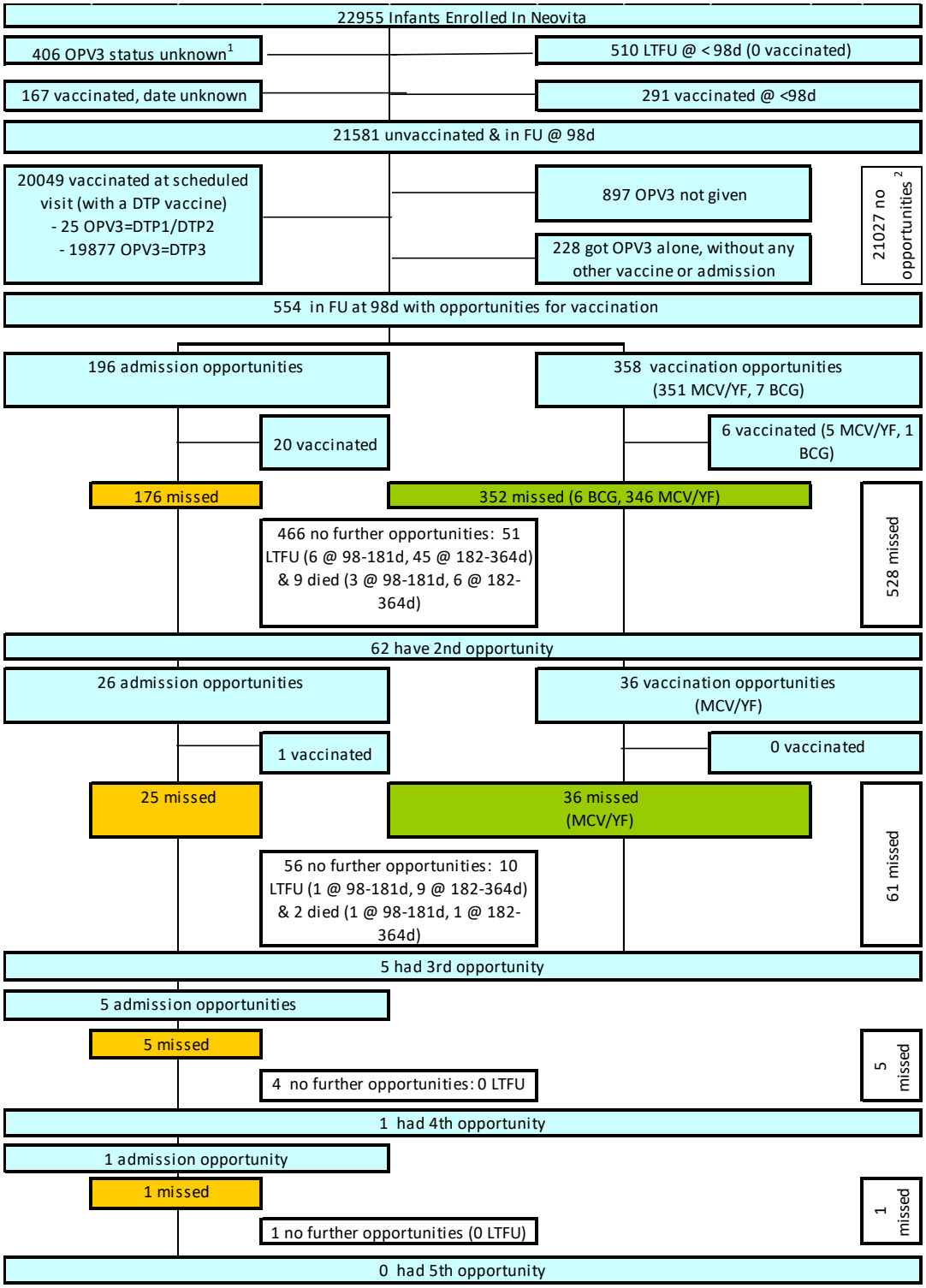


1. Of 106 BCG vaccination status unknown, 71 were LTFU (49@<28d; 14 @ 28-181d; 8 @ 182-364d), and 212 died (186 @ <28d; 24 @ 28-181d; 2 @ 182-364d; (median age@death=4d; mean =16d)

2. Of 2514 infants who got BCG alone without any other vaccines or admission, 34 got no other vaccines, 2447 got BCG before DTP1/OPV1, 26 between DTP1/OPV1 & DTP2/OPV2, 5 between DTP2/OPV2 & DTP3/OPV3, 1 after DTP2/OPV2 & no later vaccines, 1 between DTP3/OPV3 & MCV/YF

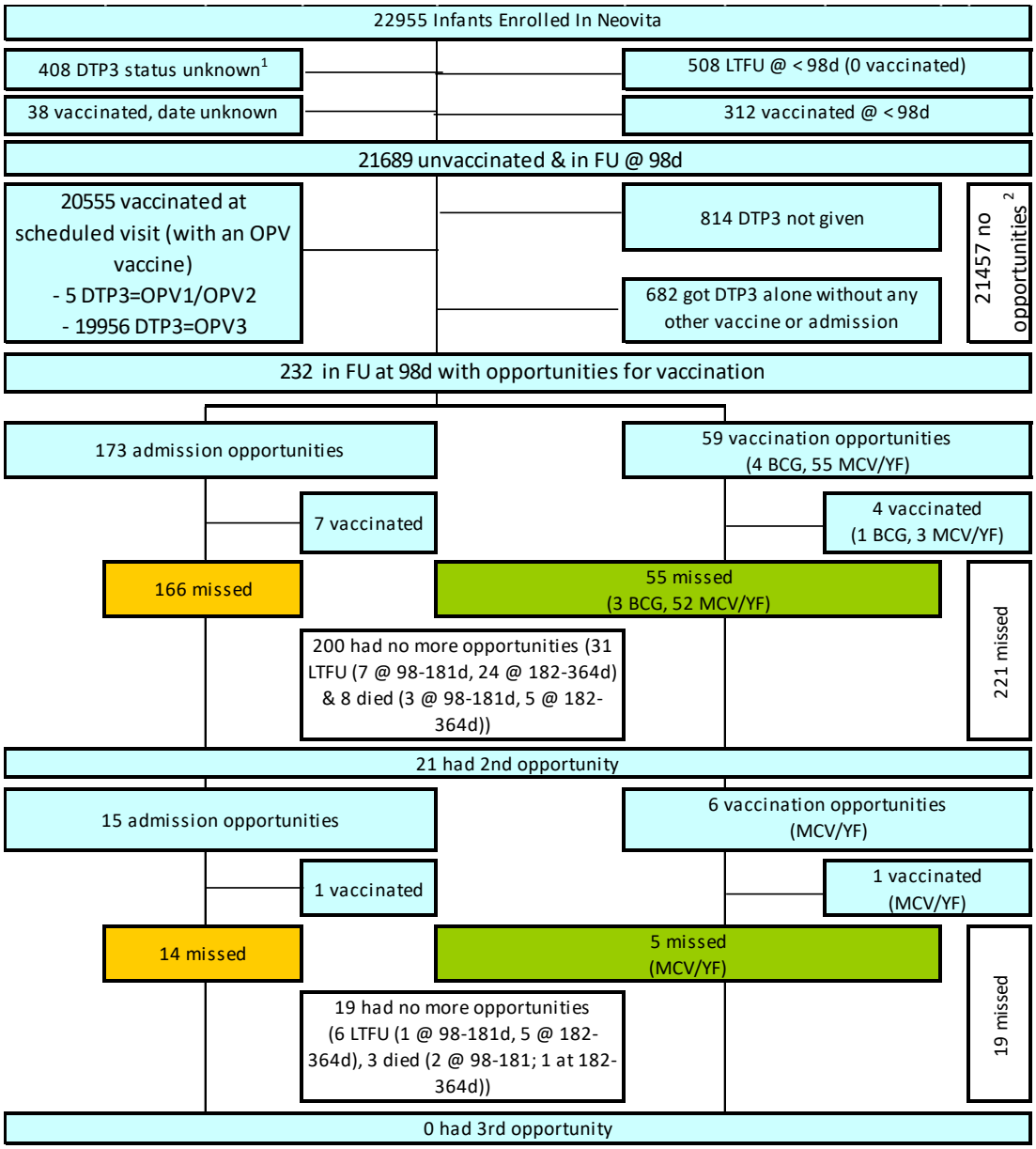
Web figure 2: Opportunities and uptake of opportunities for OPV3 vaccination



1. Of 406 OPV3 status unknown, 72 were LTFU (59 @<98d; 4 @ 98-181d; 9 @ 182-364d), and 228 died (223 @ <98d; 3 @98 - 181d; 2 @ 182-364d; (median age@death= 5d; mean =18d)

2. 556 invalid opportunities less than 4 weeks after DTP2 (all vaccine provider opportunities)

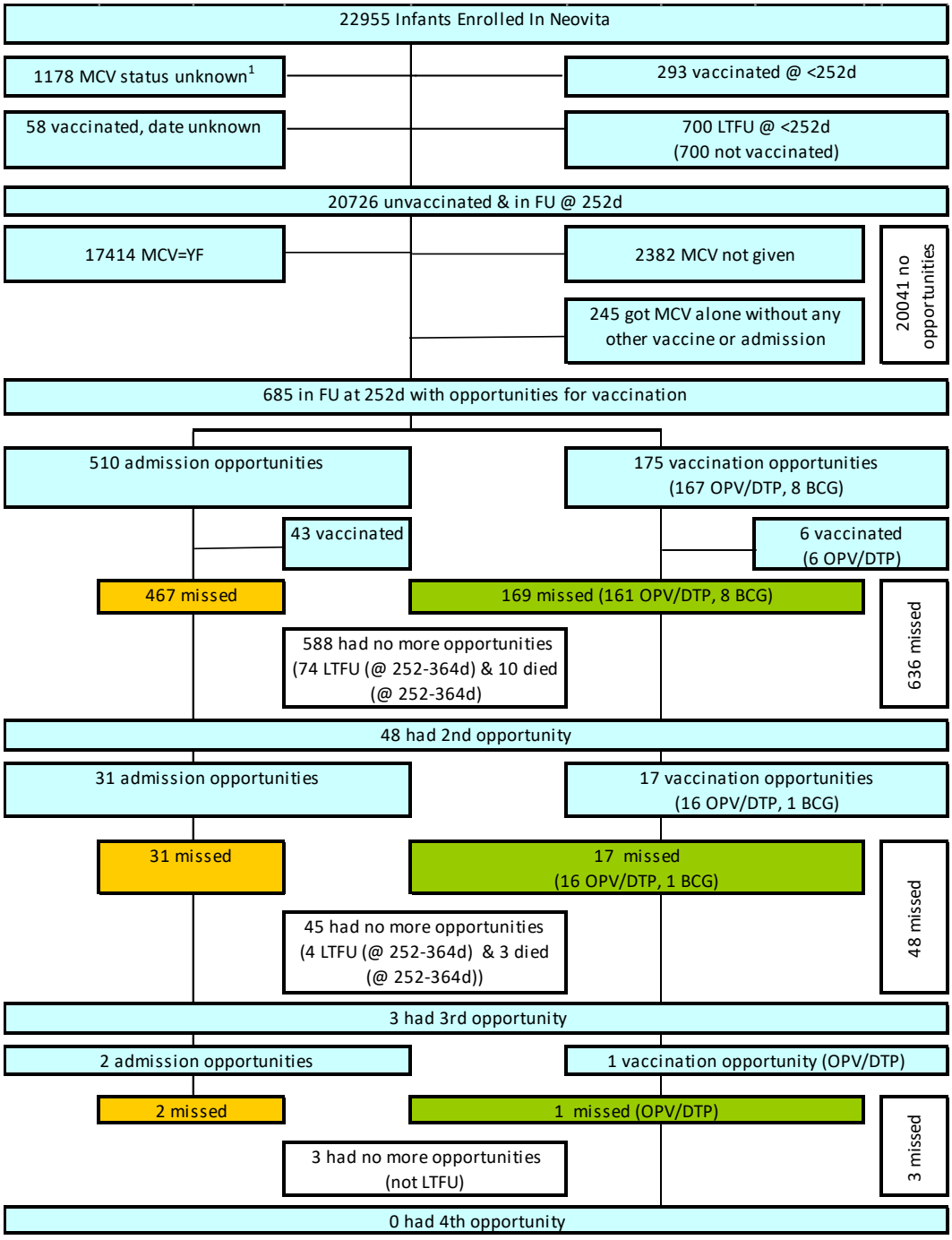
Web figure 3: Opportunities and uptake of opportunities for DTP3 vaccination



1.Of 408 DTP3 status unknown, 81 were LTFU (64 @<98d; 5 @ 98-181d; 12 @ 182-364d), and 231 died (225 @ <98d; 4 @ 98 - 181d; 2 @ 182-364d; (median age@death= 6d; mean = 21d)

2. 688 invalid opportunities less than 4 weeks after DTP2 (568 vaccine provider & 120 admission opportunities)

Web figure 4: Opportunities and uptake of opportunities for measles vaccination



1. Of 1178 measles vaccination status unknown, 840 were LTFU (836 @<252d; 4 @ 252-364d), and 235 died (@<252d (median age@death=13d; mean =53d))

7.4. HOW WOULD INCLUDING CO-SCHEDULED VACCINES AS OPPORTUNITIES FOR VACCINATION AFFECT THE ESTIMATES OF THE FREQUENCY AND UPTAKE OF OPPORTUNITIES?

As explained in **Section 7.2**, I excluded opportunities associated with co-scheduled vaccines on the basis that these vaccines are normally given together, and so I could not determine whether these opportunities would be taken automatically, or because of some action on the part of the vaccine provider to actively address under-vaccination of the infant. It is useful to consider the number and uptake of these opportunities, so as to assess the impact of this decision on my results.

I present the additional opportunities associated with co-scheduled vaccines, the uptake of these opportunities, and how including them would have changed the estimate of opportunity uptake in **Table 7.1**. For each of the included vaccines which were scheduled to be given with another vaccine (OPV3, DTP3 and MCV), inclusion of co-scheduled vaccines would have dramatically increased the number of opportunities. The uptake of these co-scheduled vaccines was in excess of 96% for each vaccine, compared to uptake rates of less than 8% for non-co-scheduled vaccines.

Table 7.1: Additional primary care-based opportunities associated with co-scheduled vaccines

Vaccine	Primary-care based opps* (excluding co-scheduled vaccines)	Uptake of primary-care based opps (%)	Additional opps associated with co-scheduled vaccines	Uptake of opps associated with co-scheduled vaccines (%)	Total opps if co-scheduled vaccines included	Opp* uptake, if co-scheduled vaccines included (%)
OPV3	394	6 (1.5)	23087	22761 (98.6)	23481	23093 (98.3)
DTP3	65	5 (7.7)	23451	22740 (96.7)	23522	22745 (96.7)
Measles	193	6 (3.1)	22926	22636 (98.7)	23119	22642 (97.9)

** Opp = opportunities; Opp = opportunity*

Including co-scheduled vaccines would have masked the poor uptake of opportunities associated with contacts for reasons other than to receive co-scheduled vaccines.

7.5. How exploiting opportunities would improve the vaccination of LBW infants

Given that this PhD aimed to investigate LBW as a risk factor for under-vaccination, and to investigate ways to improve the vaccination of LBW infants, I undertook an additional analysis (as described in **Section 7.1**) to investigate how using the opportunity to vaccinate, would improve the uptake of vaccination among LBW infants, compared to NLBW infants.

7.5.1. Methods

I repeated the analyses of the potential impact of utilising the first opportunity for vaccination on vaccine uptake at 4, 8 and 12 weeks after the vaccine due date, and at 52 weeks of age, using the same methods described in the paper, but stratified by birth weight.

7.5.2. Results

For each of BCG, OPV3, DTP3 and measles, vaccine uptake at 4, 8 and 12 weeks after the due date was generally lower among LBW compared to NLBW infants for all vaccines, although the magnitude of the difference was small, and declined with time since the due date. Exploiting the first opportunity resulted in similar improvements in uptake for both LBW and NLBW infants (**Table 7.2**). In accordance with this, I found no association between birth weight and uptake of postneonatal BCG vaccine provider opportunities (**Table 3 main paper**).

Table 7.2: Uptake rates at selected time-points associated with actual vaccination dates and with using the first opportunity to vaccinate, stratified by birth weight.

Vaccine		Actual	Theoretical
BCG	**Due date + 4 weeks**		
	>=2.5kg	47.4 (45.3-49.5)	62.2 (60.1-64.3)
	<2.5kg	42.4 (37.6-47.3)	55.3 (50.4-60.2)
	Due date + 8 weeks		
	>=2.5kg	74.0 (72.1-75.9)	91.2 (89.9-92.4)
	<2.5kg	72.3 (67.7-76.5)	88.6 (85.0-91.4)
	Due date + 12 weeks		
	>=2.5kg	83.6 (81.9-85.1)	97.3 (96.5-97.9)
	<2.5kg	80.7 (76.5-84.3)	96.7 (94.4-98.1)
	52 weeks of age		
	>=2.5kg	93.4 (92.2-94.4)	100.0 (100.0-100.0)
	<2.5kg	91.9 (88.7-94.2)	100.0 (100.0-100.0)

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OPV3	**Due date + 4 weeks**		
	>=2.5kg	2.6 (1.5-4.5)	8.1 (5.9-11.0)
	<2.5kg	0.0 (0.0-0.0)	3.5 (1.1-10.5)
	Due date + 8 weeks		
	>=2.5kg	7.9 (5.8-10.7)	15.8 (12.7-19.4)
	<2.5kg	1.2 (0.2-8.0)	8.2 (4.0-16.4)
	Due date + 12 weeks		
	>=2.5kg	13.2 (10.4-16.6)	21.3 (17.8-25.3)
	<2.5kg	8.2 (4.0-16.4)	17.6 (10.9-27.3)
	52 weeks of age		
	>=2.5kg	26.4 (22.6-30.6)	100.0 (100.0-100.0)
	<2.5kg	18.8 (11.8-28.6)	100.0 (100.0-100.0)
DTP3	**Due date + 4 weeks**		
	>=2.5kg	6.2 (3.5-10.6)	19.5 (14.5-25.7)
	<2.5kg	2.7 (0.4-17.4)	10.8 (4.0-25.9)
	Due date + 8 weeks		
	>=2.5kg	19.5 (14.5-25.7)	36.9 (30.4-44.0)
	<2.5kg	5.4 (1.3-19.6)	24.3 (13.0-40.9)
	Due date + 12 weeks		
	>=2.5kg	31.8 (25.6-38.7)	48.2 (41.2-55.3)
	<2.5kg	24.3 (13.0-40.9)	45.9 (30.5-62.2)
	52 weeks of age		
	>=2.5kg	63.6 (56.6-70.1)	100.0 (100.0-100.0)
	<2.5kg	48.9 (32.9-64.6)	100.0 (100.0-100.0)
MCV	**Due date + 4 weeks**		
	>=2.5kg	0.4 (0.1-1.4)	14.0 (11.4-17.2)
	<2.5kg	0.0 (0.0-0.0)	9.0 (5.0-15.6)
	Due date + 8 weeks		
	>=2.5kg	17.8 (14.8-21.2)	66.8 (62.8-70.6)
	<2.5kg	18.0 (12.1-25.9)	67.2 (58.4-75.0)
	Due date + 12 weeks		
	>=2.5kg	44.2 (40.2-48.4)	89.3 (86.5-91.6)
	<2.5kg	39.3 (31.0-48.3)	93.4 (87.4-96.7)
	52 weeks of age		
	>=2.5kg	60.2 (56.1-64.2)	100.0 (100.0-100.0)
	<2.5kg	58.2 (49.2-66.7)	100.0 (100.0-100.0)

7.5.3. Discussion

I have previously demonstrated that the rate of vaccination of LBW infants is lower than that of NLBW infants for DTP1 and DTP3, and that these infants are more likely to be vaccinated late (**Chapter 5**). Similarly, LBW infants were also less likely to receive BCG vaccination in the neonatal period. This under-vaccination of LBW infants may reflect parental reluctance to bring these infants for vaccination for reasons previously discussed[1]. Vaccine providers in low-income settings have previously reported hesitancy in vaccinating sick, weak and malnourished children[1]. LBW infants may be more likely to have these

characteristics in the first year of life, and so it also plausible that these infants may be more likely to miss opportunities for vaccination during their routine contacts with the health service. I found no evidence of this in my study population. The results of this analysis suggest that once a LBW infant has contact with a vaccine provider, they are as likely to receive their vaccines as NLBW infants. It appears that exploiting opportunities for vaccination is more a factor of how close the contact is to the due date for vaccination, and whether the vaccine provider remembers to check and administer all due vaccines at the visit, rather than due to any particular characteristic of the infants attending for vaccination (such as their birth weight). However, it is important to note that (unlike previous analyses in this thesis) it was not possible to stratify by gradation of LBW due to small numbers. All infants weighing less than 2.5kg at birth were analysed as a single category, and so I was unable to investigate any differential association between lower categories of birth weight and uptake of opportunities. It remains possible that uptake of opportunities could be lower for the smallest most fragile infants.

Furthermore, due to the small proportion of opportunities taken, it was not possible to undertake an analysis of the determinants of uptake of opportunities for OPV3, DTP3 or measles vaccination. Similarly, it was not possible to analyse the determinants of uptake of opportunities to vaccinate during admissions to a health facility. Consequently, I was unable to investigate further whether there was any association between birth weight and uptake of opportunities among those reporting severe illness, which necessitated an admission.

7.5.4. Conclusions and recommendations

Regardless of whether birth weight is an actual determinant of uptake of opportunities, exploiting routine contacts with health care providers would substantively improve the uptake of vaccination among LBW infants who are under-served by vaccination. Given their higher risk of delayed vaccination, vaccine providers and health care providers should be particularly vigilant in assessing their vaccination status when they have contacts with the health service, and should use these contacts to vaccinate where this is indicated.

ADDITIONAL REFERENCES FOR CHAPTER 7

1. Favin M, Steinglass R, Fields R, Banerjee K, Sawhney M. Why children are not vaccinated: a review of the grey literature. *International health* 2012; **4**(4): 229-38.

DISCUSSION

CHAPTER 8: DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS

Preamble

In this chapter, I review the key findings of the PhD, I discuss the strengths and weaknesses of the thesis, and the implications of my findings for public health policy.

8.1. KEY FINDINGS

8.1.1. LBW as a determinant of infant mortality, illness, care seeking and admissions

8.1.1.1. What was known

As detailed in **Chapter 1**, a number of studies have reported estimates for SSA of the association between either LBW, preterm delivery, or SGA and mortality. Most estimates relate to the neonatal period; population-based estimates for the postneonatal period are lacking. In particular, estimates for subgroups of LBW, such as MLBW and VLBW are lacking. Similarly, few studies have investigated the association between birth weight and illness, care seeking and health facility admissions. A number of studies have demonstrated an association between either birth weight or gestational age and hospitalisation in population-based cohorts. However, these studies were either restricted to admissions to district hospitals[1] (and so were likely to include a higher proportion of infants with severe illness than an analysis including all health facilities), or the analysis investigated admissions for particular illnesses such as RSV[2]. Studies that investigated illness or admissions[3-5], without restricting to a specific illness or to district hospitals, found no association.

8.1.1.2. What this study adds

In this study, I used data from a large population-based cohort, with low loss-to-follow up rates, and little missing data, to report estimates of the association between birth weight and mortality, illness, care seeking, and health-facility admissions in each of the neonatal, early infant and late infant periods, including for sub-categories of birth weight such as MLBW and VLBW infants.

LBW was strongly associated with increased mortality in each infant time-period. This effect was greatest for VLBW infants, who were 25.38 (95%CI:18.36-35.10) times more likely to die in the first year of life, and 48.45 (95%CI:32.81-71.55) times, 12.95 (6.30-26.60) times, and 8.42 (3.09-22.92) times more likely to die in each of the neonatal, early and late infant periods.

Although there was little evidence of an association between birth weight and illness in the first year of life, there was evidence of an association in the neonatal period for MLBW (aRR=1.57; 95%CI:1.27-1.95) and VLBW (aRR=1.58; 95%CI:1.13-2.21) infants.

There was evidence of lower care seeking for LBW infants, although this association was restricted to MLBW infants in the neonatal (aOR=3.30; 95%CI:1.98-5.48) and early infant (aOR=1.74; 95%CI:1.26-2.39) periods. This was further supported by the analysis of illnesses leading to death, where there was evidence that the parents of LBW infants were less likely to seek care for their critically ill infants and those who did seek care were less likely to do so from professional medical sources, compared to the parents of critically ill NLBW infants.

There was little evidence of an association with admissions or infection related admissions in the first year of life, and this did not vary by infant time-period.

8.1.2. Postneonatal vaccination of LBW infants in rural Ghana

8.1.2.1. What was known

Little research had been conducted into the association between birth weight and postneonatal vaccination in SSA. A single study from Guinea Bissau[6] of a cohort of LBW infants had provided indirect evidence, as it found that smaller LBW infants (those with lower anthropometric status) at two months of age were less likely to have received DTP1 than larger LBW infants (those with higher anthropometric status). Anthropometric status at age two months is likely to be influenced by a number of factors including birth weight, infant illness and infant feeding practices, and so the observed effect may not have been due to LBW alone.

8.1.2.2. What this study adds

LBW infants in Ghana were found to have lower vaccination rates than NLBW infants at up to 12 weeks after the due date. The smaller the infant at delivery the lower their rate of vaccination. This was evident for both DTP1 and DTP3, even after controlling for other determinants of delayed vaccination. For DTP1, infants weighing <1.50kg at birth had a

vaccination rate approximately 40% lower than NLBW infants at ages 10 (adjusted rate ratio (aRR)=0.58; 95%CI:0.43-0.77) and 18 (aRR=0.63; 95%CI:0.50-0.80) weeks. Infants weighing 1.50-1.99kg had vaccination rates approximately 25% lower than NLBW infants at these time points. Similar results were found for DTP3 (aRR for infants weighing <1.50kg at 22 weeks of age = 0.61 (95%CI:0.45-0.83), at 26 weeks of age = 0.60 (95%CI:0.60-0.79)).

8.1.3. Neonatal vaccination of LBW infants in Ghana.

8.1.3.1. What was known

Whilst working on this PhD, a single study was published[7], which reported that LBW infants in Kenya were more likely to be delayed in receiving BCG vaccination; however, this was a study of an urban slum population, with lower than expected rates of LBW (6%), who were almost all (96%) born in health facilities. Consequently, the results are not widely generalisable, and are certainly not generalisable to rural populations, or populations with lower rates of facility delivery. Another study[8] provided indirect evidence of an association, as it reported that undernourishment was associated with delayed BCG vaccination among children attending for vaccination at health centres in urban Nigeria. The estimates reported in this study do not represent the effect of LBW, but rather the effect of LBW plus infant feeding practices, infant illness, and other causes of undernourishment. Finally, a study from Guinea Bissau[9] reported lower BCG uptake rates for hospital born LBW infants at 18 months of age, but the authors reported a policy of delaying vaccination of LBW infants until they had either gained weight, or they attended for DTP vaccination, and so these data are not generalisable to settings where no such policy exists. In conclusion, population-based estimates on the association between LBW and neonatal vaccination for the general population were lacking, especially for rural populations.

8.1.3.2. What this study adds

This study provided further evidence that LBW is a risk factor for under-vaccination, this time in the neonatal period. There was strong evidence that LBW infants were less likely to receive BCG in the neonatal period, and, similar to the results of the analysis of postneonatal vaccination, there was a dose-response relationship between LBW and vaccination (p-trend<0.0001). Infants weighing between 1.50 and 1.99kg were 1.6 times more likely to be BCG unvaccinated by the end of the neonatal period compared to NLBW infants (aOR=1.64; 95%CI: 1.30-2.08); those weighing less than 1.50kg were 2.4 times more likely to be BCG unvaccinated (aOR=2.42; 95%CI:1.50-3.88). This effect was evident even for

infants born in health facilities (70% of the overall study population), who would automatically have opportunities for vaccination.

8.1.4. Missed opportunities for infant vaccination in Ghana, and the potential impact of their utilisation on vaccine uptake and timing.

8.1.4.1. What was known

A number of studies have investigated missed opportunities for vaccination in SSA, but most were more than 20 years old, most were descriptive in nature and most were facility-based. Population-based studies were lacking. These studies commonly reported that a large proportion of infants had missed opportunities, that a substantive proportion of opportunities occurred at a time when another vaccine was given, and that missing opportunities was more common at visits for illness than at visits for preventative care. A single 1992 study from Mozambique[10] quantitatively investigated risk factors for missed opportunities. It reported that being born in a health facility and being born to a single, divorced or widowed mother (compared to married or cohabiting) were predictors of missing opportunities. A number of qualitative and descriptive studies reported that failure to administer vaccines simultaneously, false contraindications to vaccination, fear of wasting vaccine by opening a vial for a small number of children, lack of assessment of vaccination status when the child visits a clinic, vaccine shortages, poor organisation of vaccine clinics, and a lack of a daily vaccination clinic were all factors contributing to missed opportunities. Infant illness had also been reported as a reason for missing opportunities by both mothers and vaccine providers. The association between birth weight and missing opportunities had not been studied.

8.1.4.2. What this study adds

Of eligible infants, the percentage who needed opportunities was small (50.8% (2591/5105) for BCG, 6.7% (1451/21581) for OPV3, 4.8% (1046/21689) for DTP3, 14.8% (3067/20726) for measles). Among those needing opportunities, opportunities were most common for BCG (due from birth), and most of those opportunities were associated with visits to receive OPV/DTP vaccines (scheduled between 6-14 weeks of age). There were fewer vaccination opportunities for the later scheduled OPV3, DTP3 and measles vaccines, and a higher proportion of these opportunities were facility-based. Uptake of primary-care based opportunities was highest for BCG (52%). Over 90% of primary-care based opportunities were missed for OPV3, DTP3 and measles, and >90% of facility-based opportunities were missed for all vaccines. For BCG, timing of the opportunity was the biggest predictor of

uptake. Earlier opportunities that occurred closer to the BCG due date were more likely to be taken. Compared to opportunities before age 8 weeks, uptake of BCG opportunities was 85% less likely (aOR=0.14; 95%CI:0.10-0.19) 24 weeks or more after the BCG due date. Birth weight (which due to the small number of opportunities was defined as a binary variable with LBW infants defined as weighing <2.50kg) was not a determinant of uptake of opportunities. For all vaccines, exploiting the first opportunity for vaccination would have substantively improved the uptake of vaccination (by as much as 100%) at 4, 8 and 12 weeks after the vaccine due date, and would help in reducing inequities in vaccine service delivery.

8.2. STRENGTHS AND LIMITATIONS

In chapters four to seven I discuss the strengths and limitations for the individual analyses conducted for this PhD. In this section, I consider the overall strengths and limitations of the PhD.

8.2.1. Strengths

1. *Large sample size*

A total of 22955 infants were enrolled in Neovita. This large sample size ensured that many of the analyses were highly powered to generate estimates for subgroups of the population, especially subgroups of LBW infants such as VLBW infants (**Section 3.8.4**). As data on health outcomes for VLBW infants in SSA, especially in the postneonatal period are lacking, my ability to generate such estimates is a major strength of this PhD.

2. *Frequent follow-up*

Infants enrolled in Neovita were followed-up on a monthly basis for the first year of life. This ensured the collection of highly complete data on the outcomes included in this study, and as much as possible, minimised the likelihood of erroneous recall and consequent misclassification for outcomes such as illness, care seeking, and admissions, which were based on maternal recall. Also for outcomes such as illness dates, where there was a high proportion of missing dates, the frequent follow-up visits allowed me to impute these dates with some degree of accuracy, thus minimising misclassification by time-period. For infants missing illness dates, 79% of illness dates which were reported as unknown, were reported within 30 days of the previous visit, and a further 17% were reported between 31 and 60 days after the previous visit (**Section 3.1**).

3. *High quality data on birth weight and other variables*

We collected very high quality data on birth weight for the Neovita trial. We employed a higher cadre of field worker to enrol and weigh the infants, and all of these field workers received training in measuring birth weight and in calibrating weighing scales according to a standardised protocol devised by WHO[11]. We supplied all participating health facilities with a new electronic scale at the start of the trial, which recorded birth weights to the nearest 0.1kg. Infants born at home were measured using a spring scale, which recorded birth weight to the nearest 0.2kg. Overall, 62% of infants were measured using spring scales. Scales were calibrated every four weeks. Infants were weighed between zero and 87 hours after delivery; 73% (16434) were weighed within 24 hours of delivery; 0.2% (5) of infants were weighed more than 72 hours after delivery. The high quality birth weight data was reflected in the higher proportion of infants who were classified as LBW in our study population (16% compared to a) 9% reported in the latest DHS[12] and b) 10% reported in a previous analysis of birth weight from the study area which was based on data documented in the child health card[13]).

The vaccination data collected for the Neovita trial was of very high quality and we employed a rigorous approach to resolving inconsistencies in these data, including revisiting mothers to verify the vaccination data on the card, and where necessary making copies of the vaccination card to further aid the process of resolving inconsistencies. I personally supervised this work, and I was the primary decision maker on correcting dates which were highly irregular either because they were highly inconsistent, or because they were grossly out of range.

During the trial, we collected data on a large number of variables, which allowed me to adjust my analyses for a large number of potential confounders. These data were highly complete, with fewer than 50 out of 22955 infants (approximately 0.2% of all enrolled infants) missing covariate data for the analyses. All of these data were double data entered and were subjected to a rigorous programme of range and consistency and inter-database checks during the data entry cycle, thus maximising the accuracy of the data included in my analyses.

4. *Representativeness*

Infants included in the analyses reported in this PhD were recruited from a population-based surveillance system. This will have minimised bias associated with the selection and recruitment of participants into the Neovita cohort. Consequently, the Neovita cohort were

likely to be highly representative of the underlying population, especially since recruitment was highly complete (84% of all infants born in the study area were enrolled in the trial) (**Figure 2.7, Section 2.6**). Nonetheless the representativeness of the sample and the resulting generalisability of the findings of this PhD may have been limited by a number of factors which are further discussed in **Section 8.2.2.**

5. *Low loss to follow-up and maximal retention of infants in the analyses*

The trial benefited from low loss-to-follow up rates (<3%), thus minimising bias associated with loss-to-follow up, especially since loss-to-follow-up may have been associated with vaccination status.

In addition, for the analyses of mortality, illness and vaccination timing, I maximised the retention of infants in the analyses by using person-time analyses whereby infants contributed time to the analyses for as long as they were in follow-up. This approach minimised bias where both the outcome (mortality, illness or vaccination) and the effect of the main exposure of interest (birth weight) were time varying, as discussed in **Chapters 4 and 5**.

8.2.2. Limitations

1. *Generalisability of the results*

As discussed in **Section 8.2.1,** those included in Neovita were likely to be highly representative of the underlying population. However, several factors relating to the selection of infants for inclusion in Neovita, and relating to the study population, may have affected the generalisability of the findings to the underlying population in the study area. Consequently, the strength of the associations reported in this thesis may be underestimates for the general underlying population.

Only live born infants who were able to suck or feed, who were staying in the study area for at least six months, and who were 3 days old or younger at the time of screening were enrolled in Neovita.

Among the reasons for exclusion from the trial (**Figure 2.7, Section 2.6**), infants who were missed entirely by the surveillance system (1.0%), those whose parents declined to participate (1.2%), and those whose births were ascertained too late for inclusion in the trial (2.9%), may have had characteristics (such as lower socio-economic status or poorer engagement with health services) which could have been associated with both birth weight and the outcomes measured in this PhD. These infants accounted for 5.1% of the 27330

births identified in the study area and so their exclusion was unlikely to have substantively affected the generalisability of the data.

An additional 1.4% of all live born infants were excluded either because they died before screening (1.1%) or because they were unable to feed at the time of enrolment (0.3%). Sicker, weaker infants were more likely to be excluded, as they would be more likely to have problems feeding. Those infants who were unable to feed, or who died before screening may have included a higher proportion of LBW infants. LBW infants have higher rates of illness and death in the first week of life. In addition, LBW infants may have been more likely to be erroneously classified as stillbirths, if they died shortly after delivery. Birth weight data was not available for those who died during delivery, and infants who died before screening were never weighed. Given this, the Neovita study population was likely to be healthier, and to include a lower proportion of LBW infants than the general underlying population.

Furthermore, my study population was enrolled in a randomised control trial, and this may have affected the outcomes measured in this study, specifically vaccination status, care seeking, illness, admissions and mortality. Field workers visited mothers monthly, and asked them about their infant's vaccination status and advised them to seek care for their infants if their infants were sick at the time of the visit. Their participation in the trial may have affected the mothers' health care seeking behaviour, both for vaccination, and for curative care. This may have led to overall higher rates of vaccination, care seeking and admissions, and lower rates of mortality than that experienced by the general population. I cannot confirm whether this differentially affected LBW infants or whether it affected the association between birth weight and these outcomes.

I estimated the infant mortality rate in my study population to be 30.5 per 1000 live births. This rate was lower than a) the rate of 38.0 per 1000 live births reported for Brong Ahafo in the most recent DHS[12] and b) the rate of 46.1 per 1000 live births (the sum of the reported rates for the early neonatal, late neonatal and postneonatal periods) estimated for Ghana in the 2013 Global Burden of Disease Study[14]. The lower mortality rate in the Neovita study population may be because they benefited from participation in the trial, but also because, as described above, sicker, weaker infants, and infants who died in the first three days of life were not recruited into the trial.

2. Misclassification

The data that I collected on infant illness, care seeking, and overall and infection-related admissions were based on maternal recall. Recognition of childhood illnesses in low and middle-income settings is known to be poor[15], and may be even poorer for LBW infants. This may have led to underreporting of illness and care seeking and to the misclassification of the infection-related admissions in my analyses. Unfortunately, data on the association between birth weight and recognition of illness in infancy are lacking, and so I cannot confirm whether any misclassification was differential by birth weight. As I did not have access to data on diagnoses of illness, I was not able to assess the validity of illness recall by birth weight in my study population. Given that admission to a health facility is a notable event, it is likely that minimal underreporting and misclassification of admissions will have occurred, as I would expect mothers to remember such an event.

I also relied on maternal recall to assign the vaccination status of the small percentage of infants (<1%) whose vaccination card was never seen, and whose mothers reported that they had never been vaccinated. This was to avoid automatically excluding infants who had never accessed vaccination services and who consequently never had a vaccination card. As these infants represented a very tiny proportion of infants included in the analyses, their inclusion is unlikely to have affected the association between birth weight and vaccination. For the investigation of timeliness of postneonatal vaccination, I verified this by doing a sensitivity analysis, whereby I excluded these infants. There was little difference in the results of the sensitivity analysis compared to the results of the analysis including these infants (**Section 5.6**).

Data on most of the explanatory variables included in the analyses, such as educational attainment and occupation were based on maternal report, and so may have been subject to misclassification. Data on validity of maternal report of such factors are lacking. There are no data to suggest that misreporting would be differential by birth weight.

As described in **Section 3.6** I attempted to assess possible misclassification of SES by reviewing its distribution by other markers of SES, such as maternal education and occupation, distance to the nearest health facility, and place of delivery. There was good concordance between the distributions of SES by each of these variables (**Table 3.5**). For instance, infants from the lowest category of SES had a higher proportion of mothers with no education, who were farmers, who lived >5km from a health facility, and a higher proportion of these infants were not born in a health facility. As distance to health facility

was measured by GPS (as described in **Section 3.6**), misclassification of this factor was likely to be minimal.

3. Lack of power and small numbers

As discussed in **Section 8.2.1**, my study benefited from a large sample size which allowed me to generate estimates for subgroups of the population, most notably subgroups of LBW. Nonetheless, it may be that even with this large sample, for some analyses, such as those presented in **Chapter 4** where I stratified my analyses by time period, small numbers and a lack of power may have limited the ability to demonstrate an association.

Furthermore, for the analysis of uptake of opportunities for vaccination (**Chapter 7**), the proportion of opportunities taken was small. Consequently, as discussed in **Section 7.5.3**, in my analysis of uptake of opportunities for BCG vaccination, I was unable to do an analysis by the different categories of LBW, but rather I had to analyse the effect of birth weight modelled as a binary variable (with LBW defined as infants weighing <2.50kg). I was therefore unable to investigate any differential association between lower categories of birth weight and uptake of opportunities. Similarly, due to small numbers, I was unable to analyse uptake of opportunities for OPV3, DTP3 or measles vaccination, and I was unable to analyse uptake of opportunities associated with health facility admissions.

4. Multiple testing

I adjusted for a large number of variables in all of my models, and so it is possible that some associations reported in this PhD will have occurred by chance alone (due to type 1 error). This thesis tested hypotheses that were developed a priori and that were biologically and socially plausible. The development of these hypotheses was informed by evidence from other settings. Many of the effect sizes, including those for LBW, were large, with very small p-values, lessening the likelihood of type 1 errors.

5. Outstanding unanswered questions

A number of key questions remain unanswered at the end of this PhD due to limitations in the availability of some key data.

Although data on LMP were collected for the PhD, these data were missing for almost 60% of pregnancies, and were inconsistently reported for a further 16% of pregnancies. Given the poor quality of the Neovita data on LMP, and given the well-documented limitations of using LMP to estimate gestational age[16-18], I was unable to differentiate between the varying effects of gestational age and intrauterine growth retardation (**as discussed in**

Section 1.6) for this PhD. This would have allowed a better characterisation of the risk based on levels of prematurity and growth retardation, which could inform the development of more targeted interventions.

Furthermore, I was unable to adjust my estimates of the association between birth weight and mortality and illness for the mediating effects of breast-feeding, due to the lack of complete data on breast-feeding, and the likely reverse causality between illness and feeding (**Section 4.3**). As breastfeeding is protective against mortality[19] and illness[20,21], if LBW infants had lower rates of breastfeeding, this may partially explain the association between birth weight and these outcomes.

My analyses of the association between birth weight and mortality, illness, care seeking and admissions (**Chapter 4**) were further limited by a lack of data on a number of important factors including 1) illness recognition, 2) severity of illness, 3) time to care seeking, and 4) where and from whom care was sought (except for hospital admissions). These factors may have differed among LBW infants compared to NLBW infants and may have partially explained why the excessive mortality rates among LBW infants compared to NLBW infants were not mirrored by corresponding excessive rates of illness and admissions. For instance, poorer recognition of illness among LBW infants would lead to underreporting of illness, to no or delayed care seeking for these infants, and it could affect their admission rates. A propensity to more severe illness or rapidly progressing illness in LBW infants may affect their risk of mortality. If the parents of LBW infants were more likely to seek care from traditional healers (perhaps because the infant was deemed to have a not-for-hospital illness (as discussed in **Chapter 4**), this would affect their admission rates and risk of mortality. The absence of data on these factors limited my ability to fully investigate the association between birth weight and infant illness, care seeking and care giving, and how these relate to infant mortality.

I also lacked data on clinical diagnoses for cause of admissions and on illnesses due to VPDs, as I did not have access to the infants' medical records. I was therefore unable to investigate the association between birth weight and cause-specific illness (other than a broad analysis restricted to infection-related admissions to minimise potential misclassification due to erroneous maternal recall). I was unable to investigate whether LBW infants were at increased risk of VPDs, or whether delayed vaccination of LBW infants was associated with an increased risk of VPDs. Similarly, I lacked data on physician-coded cause of death, and was therefore unable to investigate whether LBW infants were at

increased risk of dying from vaccine preventable or infectious diseases. Consequently, I was unable to investigate the clinical significance of timely vaccination among LBW infants.

Finally, this PhD would have benefited from the availability of qualitative data on parental and vaccine provider knowledge, attitudes and practices relating to the vaccination and uptake of opportunities for vaccination among LBW and NLBW infants. Although I found convincing evidence that LBW infants are less likely to be vaccinated in both the neonatal and postneonatal periods, I was unable to investigate why they were less likely to be vaccinated, or to identify any perceived barriers or erroneous beliefs or attitudes relating to their vaccination among either parents or vaccine providers. Similarly, I was unable to investigate the reasons for missing opportunities for vaccination, for either primary care based or facility-based opportunities. A lack of data on the reasons driving the under-vaccination of LBW infants and the lack of uptake of opportunities limits the ability to identify specific interventions to address these two issues.

8.3. IMPLICATIONS OF FINDINGS

This PhD addresses a number of key questions relating to infant health outcomes for LBW infants in SSA, which to date have not been widely studied and for which data are lacking. It presents the results of an in-depth investigation into the association between birth weight and infant vaccination, and it demonstrates that LBW infants are a group that are under-served by vaccination, both in the neonatal and postneonatal period, with a strong dose response relationship between birth weight and vaccination.

As discussed in **Section 1.4**, timeliness of vaccination is increasingly recognised as an important indicator of the overall quality of vaccination programmes[22]. Furthermore, as discussed in **Section 1.5**, the Global Vaccine Action Plan[23] advocates for identifying groups who are under-served by routine vaccination services so that they can be targeted for vaccination. The potential of vaccination to reduce child mortality has yet to be fully realised. Substantive inequities in the delivery of vaccines remain[23]. Improving equitable access to vaccination will help to address health inequalities and to maximise the effectiveness and impact of vaccination. It is also critical to address disease elimination and eradication targets[23]. The results reported in this PhD of delayed BCG and DTP vaccination, including among infants born in health facilities, and among LBW infants, highlights an area of underperformance in the routine childhood vaccination programme and highlights an inequity in vaccine delivery.

Delayed vaccination of LBW infants matters. As with any infant who experiences delayed vaccination, this will unnecessarily prolong their risk of contracting a VPD. As discussed in **Chapter 1**, in 2013, three out of every ten deaths among children aged one to 59 months were estimated to be due to VPDs[24], and SSA carries a higher burden of VPDs than other regions[25]. Given their elevated mortality rates (as demonstrated in **Chapter 4**), every effort should be taken to minimise their risk of illness and death, including maximising their access to preventative care services such as vaccination.

As discussed in **Section 1.7**, there are a number of reasons why adherence to the timing and staging of vaccination may be more important among LBW infants. These include lower levels of maternal antibodies[26,27], lower antibody response to vaccination[28], lower persistence of antibodies[28], and increased susceptibility to the complications of VPDs due to conditions associated with LBW such as bronchopulmonary dysplasia[29]. Whereas some studies from high-income settings have reported an increased risk of hospitalisation and death among LBW and preterm infants for VPDs that are most prevalent early in infancy[29-32,33], there is a lack of data on the risk of VPDs among LBW infants in SSA (as discussed in **Section 1.6).** Overall, the clinical implications of delayed vaccination for LBW infants in SSA are unknown, but there is every reason to believe that the clinical implications are the same as for LBW infants in high-income settings.

Interventions should be targeted at LBW infants to improve their timeliness of vaccination. Improving the vaccination of LBW infants will help to improve the overall performance of the vaccination programme, and will address an inequity in the programme. However the identification of such infants may be challenging, as almost 50% of infants in low income settings are not weighed at birth[34] (as discussed in **Section 1.6.2**). This limits the ability to use birth weight itself as a marker for under-vaccination. Infants who are not weighed are also likely to have other risk factors for non-vaccination, such as being born to mothers with lower socio-economic status and educational attainment, and being born at home[34-36]. Given this, it is important not to restrict the findings of this thesis to infants meeting strictly defined cut-offs of birth weight, but rather to extrapolate them to include fragile infants who may be missing data on their birth weight, and whose first encounter with the health service may be some time after delivery.

I reported some evidence that LBW infants were as likely to be vaccinated as NLBW infants when they had opportunities for vaccination, although these results should be interpreted with caution as birth weight was modelled as a binary variable, and the analysis was limited

by small numbers (as discussed in **Sections 7.5.3 and 8.2.2**). It may be that delayed vaccination of LBW infants is largely driven by parental hesitancy to take LBW infants for vaccination. Nonetheless some practices by vaccine providers, such as not vaccinating facility born infants prior to discharge, may be contributing to inequitable uptake of neonatal vaccination by LBW infants, as birth weight remains a risk factor for non-vaccination in the neonatal period, even among facility born infants.

Attending for vaccination represents a contact with the health service, and so it provides an opportunity to access general medical care for an infant. Poorer access to vaccination services among LBW infants will result in them having fewer contacts for care in general. If this is the case, then this is occurring within the context of broader poorer health outcomes for these infants, including a dramatically increased risk of dying throughout the first year of life, a possible increased risk of illness, and lower rates of care seeking for sick LBW infants. This demonstrates a need for the promotion of health care seeking behaviour for these infants.

Currently there is great emphasis on developing strategies to minimise mortality and illness among LBW infants in the neonatal period, as this is the time-period when most infant deaths occur. However, my analyses demonstrate that LBW infants remain at risk throughout the first year of life, and so it highlights the importance of maximising preventative and curative care for LBW infants throughout this time-period.

8.4. RECOMMENDATIONS

In this section, I outline a number of recommendations indicated by the findings of this PhD. These recommendations aim to:

1. Improve the uptake and timing of vaccination among LBW infants
2. Clarify policy relating to the vaccination of LBW infants
3. Improve LBW infant survival and reduce their risk of illness throughout the first year of life
4. Reduce LBW infants inequitable access to health care when they are sick
5. Improve the uptake of opportunities for vaccination among the under-vaccinated

6. Address gaps in the knowledge base relating to a) the reasons for under-vaccination of LBW infants, and b) the relationship between illness, care seeking and mortality among LBW infants.

8.4.1. Policy recommendations directed at health care providers and care givers

1. Health care providers should be educated to ensure that LBW infants who are born in health facilities receive all their due vaccinations prior to discharge.

2. Health care providers and vaccine providers should be encouraged to counsel caregivers about the importance of vaccinating LBW infants on time, and to assure them that birth weight and infant illness are not contraindications to vaccination.

3. Caregivers of LBW infants should be encouraged to improve their care seeking practices for LBW infants, throughout the first year of life.

4. Health care providers should be trained to verify an infant's vaccination status at all health care contacts (both primary-care based and facility-based), and to administer all due vaccines, in order to improve overall vaccine uptake.

8.4.2. National and International Policy Recommendations

1. Strategies to minimise illness and mortality among LBW infants throughout the first year of life (including both the neonatal and postneonatal periods) should be developed as a matter of priority.

2. The Ghanaian Ministry of Health should stipulate in their national policy guidelines on vaccination that LBW is not a contraindication to vaccination and that all infants should be vaccinated in accordance with the routine schedule regardless of their gestational age or size.

3. Similarly, the WHO should stipulate in its vaccination policy documents (as it previously did) that neither preterm delivery nor LBW are contraindications to vaccination.

8.4.3. Recommendations for research

1. Further research into the barriers and facilitators of vaccination of LBW infants is warranted. This should include qualitative research among care givers and vaccine providers to further understand the reasons for delayed or non-vaccination among LBW infants

2. Strategies to improve the uptake and timing of vaccination among LBW infants should be developed and these strategies should be evaluated

3. Further research into illness and pathways of care among LBW compared to NLBW infants, and their association with mortality in SSA is warranted. This will enable a better understanding of why the higher mortality rates reported among LBW infants do not appear to correspond to higher illness rates.

8.5. CONCLUSIONS

LBW infants are an under-served group for vaccination in Ghana. They are also at greatly increased risk of mortality throughout the first year of life, and somewhat at increased risk of illness. Their lower access to vaccination services is reflected in lower access to care during illness, which suggests that these infants are generally disadvantaged when it comes to both preventative and curative care seeking. Efforts to maximise their access to health care services, including vaccination are warranted in order to increase their chances of survival.

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ANNEX 1: SEARCH TERMS USED TO REVIEW THE LITERATURE

1. Birth weight and vaccination

(((low birth weight) OR (premature) OR (pre-term) OR (preterm) OR (underweight) OR (intra-uterine growth retardation) OR (intra-uterine growth restriction) OR (intra uterine growth restriction) OR (intra uterine growth retardation) OR (small for gestational age)) AND ((newborn) OR (neonate) OR (infant) OR (baby) OR (babies)) AND ((vaccine#) OR (immunization) OR (immunisation)) AND ((uptake) OR (coverage) OR (missed opportunities) OR (opportunities) OR (timeliness) OR (time) OR (delay#) OR (age appropriate) OR (age-appropriate) OR (adherence) OR (compliance)))

2. Birth weight and mortality, illness, care seeking and admissions

(((low birth weight) OR (premature) OR (pre-term) OR (preterm) OR (underweight) OR (intra-uterine growth retardation) OR (intra-uterine growth restriction) OR (intra uterine growth restriction) OR (intra uterine growth retardation) OR (small for gestational age)) AND ((newborn) OR (neonat*) OR (postneonat*) OR (infant) OR (under-five) OR (under five) OR (under-5) OR (under 5) OR (child) OR (baby)) AND ((death) OR (mortality) OR (disease*) OR (care) OR (careseek*) OR (caregiv*) OR (sick*) OR (infectio*) OR (hospitali#tion) OR (admission) OR (admitted OR (illness) OR (ill) OR (morbidity)) AND (afric*)))

ANNEX 2: NEOVITA DATA COLLECTION FORMS

KINTAMPO HEALTH RESEARCH CENTRE NEOVITA TRIAL ENROLMENT FORM 22 JUNE 2010	ENROL Form No.	FORMNO

FILL ONE FORM FOR EACH BIRTH NOTIFIED EVEN IF MULTIPLE BIRTH OR BABY DIED BEFORE DOSING

1. SCREENING INFORMATION

1.1 Site of screening ……	11. Compound	12. Facility	13. Other specify	PLACESCR
1.1.1. If facility, please state facility code (NA = 99) ..…….				FACSCR
1.1.2. If compound, please provide compound number (NA = 99999999)……				COMPSCR
1.1.3.If other, please specify …..				OTHSCR
1.2 Mother's name ……...				WOMNAME
1.3 Mother's Neovita id ……..……..……				WOMANID
1.4 Date of visit (dd/mm/yyyy)…….……				DATESCR
1.5 Staff code ……...……..……...				FW
1.6 Is the mother alive? ……..……...……	1. Yes	2. No		MOALIVE
1.7 Who is the respondent for this interview?.....	11. Mother of baby	12. Father of baby	13. Other family member / 14. Other guardian / caretaker	INFORMANT

2. CONSENT

PLEASE READ OUT THE MAIN STUDY INFORMATION SHEET AND CONSENT FORM

2.1 Does the mother/caretaker give consent for?

11. Full participation in study including dosing and follow-up	12. Only for completing this and baseline form	ICONSENT
13. No, does not give consent but baby alive	14. No, does not give consent and baby died	

IF ANSWER IS 11, FILL OUT THE REST OF THIS FORM AND THE BASELINE FORM AND DOSE THE BABY

IF ANSWER IS 12, DO NOT DOSE BABY PUT A DOUBLE LINE THROUGH SECTIONS 3-5, AND FILL OUT SECTION 6 AND BASELINE FORM ONLY

IF ANSWER IS 13 OR 14, END THE INTERVIEW AND DRAW A DOUBLE LINE THROUGH REST OF FORM

3. ELIGBILITY

3.1. Date of delivery (dd/mm/yyyy)…….……		DATEBIRTH
3.2 Time of delivery (24 hour clock)…….....……..		TIMEBIRTH

NOW LOOK AT DOB AND TODAY'S DATE. IF THE BABY WAS BORN TODAY, YESTERDAY OR DAY BEFORE YESTERDAY THE BABY IS AGE ELIGIBLE AND THE ANSWER TO QUESTION 3.3 IS 1.YES.

IF THE BABY IS NOT BORN ON THOSE DAYS THEN THE ANSWER TO QUESTION 3.3 IS 2/NO

3.3 Is the baby age eligible for enrolment? ……...…….	1. Yes	2. No	AGEELIG

3.4 Is the infant able to breastfeed or drink other fluids?

	01. Yes	02. No	11. Cannot assess as infant is too ill / admitted in hospital	FEED
	12. Cannot assess as baby died		13. Cannot assess for other reason(s)	
3.4.1.If other reasons for not feeding, please specify				OTHFEED

3.5 Will the infant stay in the study area for the next 6 months? ……	1. Yes	2. No	STAY

ONLY PROCEED IF Q3.3-3.5 ARE 1/YES. OTHERWISE END HERE PUT DOUBLE LINE THROUGH Q3.6-Q3.11 AND MOVE TO Q3.12

NOW DETERMINE IF THERE IS CLEAR WRITTEN INFORMATION ABOUT THE MOTHER'S COMPOUND NUMBER. IF NO CLEAR WRITTEN INFORMATION THEN YOU MUST FIND OUT THIS INFORMATION BEFORE COMPLETING REST OF FORM (EG ASK FAMILY TO FETCH ANC CARD OR FOLLOW MOTHER HOME).
PLEASE PASS THIS FORM TO THE TRACKING TEAM OR DOSING COORDINATOR IF NECESSARY

3.6 Was the form passed to a member of the tracking team? ……..……..…….	1. Yes	2. No	TRACK
3.7 If yes, staff code of tracking team member 99=NA……..……			TRACKFW
3.8 Is there clear written information about the mother's compound number? ……..…	1. Yes	2. No	CLEARAD

3.9 What is the source of the mother's compound number?

11. Id card	12. Written on paper e.g. on ANC card	13. Written on compound building	SOURCE
14. Other specify		99. NA, No clear address	

3.10 What is this compound number? ……..….. (NA = 99999999)									COMPNO

3.11 Is this the mother's

11. Usual/permanent Residence	12. Her mother's compound	13. The compound of another friend or relative	COMPTYPE
14. Other specify		99. NA, no clear address	

3.12. **BASED ON THE INFORMATION ABOVE, PLEASE DECIDE IF THE BABY IS ELIGIBLE FOR THE STUDY**
(THE BABY IS ELIGIBLE IF THE ANSWERS TO 3.3, 3.4, 3.5. 3.8 ARE 1/YES)

1. Yes	2. No	ELIGIBLE

IF BABY IS ELIGIBLE (Q3.12=1/YES), THEN ENROL BABY AND FILL OUT THE REST OF THIS FORM.
IF BABY IS NOT ELIGIBLE (Q3.12=2/NO), THEN DO NOT ENROL BABY PUT A DOUBLE LINE THROUGH SECTIONS 4 AND 5 AND MOVE TO SECTION 6

PRIOR TO DOSING, CONFIRM THAT THE BABY WAS NOT BORN IN THE PREVIOUS 2 HOURS. IF BORN IN THE PREVIOUS 2 HOURS, DO NOT ADMINISTER THE SUPPLEMENT. TAKE AN APPOINTMENT AND COME BACK LATER. IF 2 HOURS HAVE PASSED, YOU CAN ENROL AND DOSE THE BABY

4. ENROLMENT AND DOSING

FIRST CHECK IF THIS WAS A MULTIPLE BIRTH

4.1.1 How many babies were born 99=NA……..			NUMBABY
4.1.2 How many babies were enrolled 99=NA……..			NUMENROL

4.1.3. If multiple birth, did this baby come out of the womb first, second or third

11. First born	12. Second born	13. Third born	99. NA	ORDERB

FIRST ID GOES TO FIRST BORN (EG 100005), SECOND ID TO SECOND BORN (EG 100006), THIRD ID TO THIRD BORN (100007)

4.2 Subject id …..……

[PLEASE STICK LABEL FROM THE CAPSULE STRIP ON THE FORM]

						SUBJECTID

4.3 This infant's name … | | INAME

USE DAY NAME IF NECESSARY BUT ALSO WRITE TWIN ONE, TWIN TWO FOR TWINS

ALSO COMPLETE A NEOVITA ID CARD WITH ONE OF THE LABELS FROM THE CAPSULE STRIP AND FILL OUT THE BABY'S DETAILS. YOU MUST USE THE MOTHERS EXISTING NEOVITA ID CARD WHEREEVER POSSIBLE. FILL OUT TWO CARDS FOR TWINS AND THREE CARDS FOR TRIPLETS.

NOW PLEASE DOSE THE INFANT BUT WASH YOUR HANDS FIRST

4.4 Was the first capsule administered to the baby? ……	1. Yes	2. No	DOSING
4.5 Did the baby swallow the capsule contents successfully? ……..……..	1. Yes	2. No	SUCCESS
4.6 Did the infant spit or vomit the dose? ……	1. Yes	2. No	VOMITTED

4.7 Date of administration (dd/mm/yyyy)……									DATEDOSE
4.8 Time of administration (24 hour clock)…….……									TIMEDOSE

4.9 Did the DS drop or spill the contents of the capsule? ……	1. Yes	2. No	9. NA	SPILL

DO NOT ADMINISTER THE BACKUP CAPSULE IF THE INFANT SPITS OR VOMITS BECAUSE THE INFANT IS STILL CONSIDERED TO HAVE RECEIVED THE DOSE.
ONLY ADMINISTER THE BACK UP CAPSULE IF YOU DROP THE CONTENTS OR CAPSULE AFTER CUTTING. IE IF Q 4.9 WAS 1/YES

4.10 Was the backup capsule administered? ……	1. Yes	2. No	9. NA	BACKUPCAP

4.11 Site of dosing ……..	11. Compound	12. Facility	13. Other specify	PLACEDOSE
4.12.If other, please specify ……..…				OTHDOSE

4.13. If facility, please state facility code (NA = 99) ..……		FACDOSE

4.14. If compound, please provide compound number (NA = 99999999)										COMPDOSE

4.15 Specify any other problems in administration of capsule

	PROBLEMS

5. FOLLOW UP INFORMATION
PLEASE INFORM THE MOTHER THAT THE BABY WILL BE VISITED TOMORROW
FULL INFORMATION IS NEEDED THAT WILL HELP LOCATE THE BABY TOMORROW

5.1 Please record the mothers phone no											
5.2 Please record any other useful phone nos…….……..											

5.3 Where will the baby be tomorrow?	11. Facility	12. This compound	13. Other compound	LOCATIONF
5.4 Village/town name				VILLNAMEF

5.5 Village/town code……				VILLCODEF
5.6 If facility, please state facility code (NA = 99)….……..…….				FACCODEF

5.7If another compound, please provide compound number (NA = 99999999, NK = 888888888)									ANCOMPF

5.8 Please provide full details about how to locate the baby tomorrow

6. ADDITIONAL INFORMATION ABOUT THE BABY

6.1 What was the sex of the baby? ……..……	11. Male	12. Female		SEX
6.2 Was the baby put to breast or breastfed before dosing? ……..……	1. Yes	2. No	9..NA died	BFDOSE
6.3 Was the baby given any other fluids or food before dosing? ……..……	1. Yes	2. No	9..NA died	OTHDOSE
6.4 If yes Specify				OTHBEFORE
6.5 Has the baby been put to breast or breastfed since birth? ...…….……	1. Yes	2. No		BFED
6.6 How many hours after birth did you put the baby to the breast? …… (NA, have not yet put baby to breast = 99)				BFSTART

6.7 Since birth, has the baby been offered anything else [PROMPT]:

6.7.1	Breast milk from another mother? ……	1. Yes	2. No	8. NK	WETNURSE
6.7.2	Any other milk other than breast milk such as tinned, powdered, or fresh animal milk or commercially produced infant formula	1. Yes	2. No	8. NK	OTHMILK
6.7.3	Water ……	1. Yes	2. No	8. NK	WATER
6.7.4	Medicines, vitamins or ORS ……	1. Yes	2. No	8. NK	MEDICIN
6.7.5	Other water based fluids [PROMPT for: water, juice, tea, sugar, glucose, traditional medicines] ……...	1. Yes	2. No	8. NK	OTHFLUID
6.7.6	Any foods [PROMPT for: any solid foods, porridge, bread, rice, cerelac, nutrimix]? ……...	1. Yes	2. No	8. NK	SOLID
6.7.7	Has baby been given colostrum? ……..……	1. Yes	2. No	8.NK	COLOSTRUM

NOW A KHRC STAFF MEMBER MUST EITHER WEIGH THE BABY THEMSELVES OR DIRECTLY SUPERVISE THE WEIGHING. IF THE WEIGHT HAS BEEN UNSUPERVISED THEN IT MUST BE REPEATED.

6.8.1 Who weighed the baby?

12. Dosing supervisor	13. Other KHRC staff Specify:_____	14. Doctor	15. Nurse	16. CHO	WHOWT
17. CBSV	18. Other health professional staff (eg TBA) Specify:_____	19. Other person Specify:_____	99. NA (i.e. not weighed)		

6.8.2 If KHRC staff, provide the staff code of the person who weighed the baby (99=NA)……..……..		CODEWT
6.8.3 Date baby weighed (dd/mm/yyyy)…….		KBWTDATE
6.8.4 Time baby weighed (24 hour clock) 8888=NK……		KBWTTIME
6.8.5 Weight of baby (in kg) 9.99 = NA.....	•	WEIGHT

6.8.6 What scales were used?

11. Digital KHRC scales	12. Salter spring KHRC scales	13. Other Scales Specify:_____	SCALE

6.9 If the baby was not dosed, what was the reason for not dosing the baby?

99. Not applicable, baby was dosed	11. Baby died before dosing	NOTDOSED

12. Baby was enrolled in another study. Please specify study.	13. Mother did not give consent for dosing
14. Baby not age eligible for enrolment	15. Baby unable to feed
16. Baby will not remain in the study area for 6 months	17. Other reason, please specify:

7. How many months pregnant where you when you delivered? (88 = NK)…… | | | GESTATE

END OF ENROLMENT FORM, THANK THE RESPONDENT CHECK FORM AND FILL BASELINE FORM

KINTAMPO HEALTH RESEARCH CENTRE NEOVITA TRIAL **BASELINE FORM** 24 JUNE 2010, v1.0	**BASELINE Form No.**	FORMNO

1. BACKGROUND and ID

1.1 Site of visit ……..	11. Compound	12. Facility	13. Other specify	PLACEB
1.1.1. If facility, please state facility code (NA = 99) ..…….				FACSCR
1.1.2. If compound, please provide compound number (NA = 99999999)				COMPB
1.1.3.If other, please specify …				OTHSB
1.2 Mother's name ……...				WOMNAME
1.3 Mother's Neovita id ….……				WOMANID
1.4 Date of visit (dd/mm/yyyy)……..……				DATEVISIT
1.5 Staff code ……...……..……...				FW

2. DELIVERY INFORMATION

2.1 Please provide the date of delivery (dd/mm/yyyy) (NA=999999)				DATEDEL
2.2 How many babies were born ……	11. Single birth	12. Twins	13. Triplets	SINGELTON
2.3 How many babies were enrolled in the Neovita study 99=NA……...…..……..				NUMENROL
2.3.1 Infantid (NA = 999999) ……..……				SUBJECTID1
2.3.2 Infantid (NA = 999999) ……..…				SUBJECTID2
2.3.3 Infantid (NA = 999999) …….				SUBJECTID3
2.4 Place of birth ……..	11. Compound	12. Facility	13. Other specify	PLACEBIR
2.4.1. If facility, please state facility code (NA = 99) ..…….				FACBIR
2.4.3. If compound, please provide compound number (NK=88888888 NA = 99999999)				COMPBIR
2.4.4.If other, please specify ……..…				BIRTHOTH

PLEASE ASK THE MOTHER

2.5 What was the type of delivery?.....	11. Normal	12. Assisted eg forceps	13. Caesarean	TYPEDEL

2.6 Who conducted the delivery?

11. Doctor	12. Nurse or midwife	14. TBA trained or untrained	15. Community health officer	ATTENDT
19. Other health professional, Specify	16. Relative	17. Neighbour or friend	18. None, woman herself	

2.7 Was the baby born …….....	11. On time or on due date	12. Early or before due date	13. Late or after due date		PRETERM
2.8 Do you know when you had your last menstrual period? ……..……			1. Yes	2. No	LMPKNOW

2.9 If YES, what was the first day of the last menstrual period: (dd/mm/yyyy) (08/08/0808=NK, 09/09/0909 =NA)

								LMP

3. MOTHER'S DETAILS

3.1 How many living children do you have, not including this current child? ……				ALIVENO
3.2 Have any of your children died? ……..……	1. Yes	2. No		CHDIED
3.3 If yes, how many of your children have died? (NA = 99) ……..…..……				DIEDNO
3.4 Did you have any health problems in the year BEFORE you were pregnant?.....	1. Yes	2. No		HEALTHY
3.5 If YES, specify				HEALTHS
3.6 Were you enrolled in the Obaapavita Trial? …...……..……	1. Yes	2. No	8. NK	OBVITA
3.7 Did you receive other vitamin A supplements before delivery? ……..…	1. Yes	2. No	8. NK	ANSUPPL
3.8 If YES, how many months before delivery? (NA = 99, NK = 88)….....				MOSUPPL
3.9 Did you receive vitamin A megadose after delivery?.....	1. Yes	2.No	8. NK	PNSUPPL
3.10 If YES, how many days after delivery? (NA = 99, NK = 88)….....				DAYSUPPL
3.11 What is your age? (NA = 99, NK = 88)....……..……..……...				MOTHERAGE

3.12 PLACE THE WOMAN IN ONE OF THE FOLLOWING AGE GROUPS:

11.15-19 years	12. 20-24 years	13. 25-29 years	14. 30 – 34 years	AGEGRP
15. 35-39 years	16. 40-44 years	17. 45-49 years	88. NK	

3.13.1 For how many years did you go to school? (00=None, 88=NK)…….…… | | | MOTHEREDU

3.13.2. What was your highest educational level completed?

1. None	2. Primary school	3. Middle,continuation school, JSS	4. Technical, commercial, SSS, Secondary school	MEDLEV
5. Post-middle college, secretarial	6. Post secondary, nursing, polytechnic	7. University	8. Not known	

3.14 What is your occupation?

11. Government employee	12. Private employee	14. Self employed		MOTHEROCC
15. Farming only	16. Does not work	17. Other	99. NA	

3.15 If occupation of woman is 'other' then specify

	MOCCO

4. HOUSEHOLD CHARACTERISTICS

PLEASE EXPLAIN TO THE MOTHER WHAT A HOUSEHOLD IS

4.1 Who is the head of your household?

11. Mother of baby	12. Father of baby	13. Grandmother of baby	14. Grandfather of baby	HEAD

15. Other specify:

4.2 How many years of schooling has the head of household (00=None, 88=NK)……

		FATHEREDU

4.2.1. What was the highest educational level completed for the household head?

				HHMEDLEV
1. None	2. Primary school	3. Middle,continuation school, JSS	4. Technical, commercial, SSS, Secondary school	
5. Post-middle college, secretarial	6. Post secondary, nursing, polytechnic	7. University	8. Not known	

4.3 What is the occupation of head of household?

				FATHEROCC
11. Government employee	12. Private employee	13. Self employed		
14. Farming only	15. Does not work	16. Other	99. NA	

4.4 If occupation of head of household is 'other' then specify

	FOCCOTH

4.5 Is the head of the household staying with the family? .....

1. Yes	2. No	FATHSTAY

4.6 What is the main source of drinking water for members of your household?

				HOUSEWTR
11. Piped water into dwelling	12. Public tap	13. Hand pump or closed borehole	14. Open well	
15. Closed well	16. Tanker truck	17. Small cart with tank	18. Surface water (river / dam / lake / pond / stream / canal / irrigation channel)	
19. Bottled water	20. Rain water		21. Other	

4.7 If source of water is 'other' then specify

	WTROTHER

4.8 What kind of toilet facility do members of your household usually use?

			TOILET
11. Flush or pour flush toilet	12. Pit latrine	13. Dry toilet	
14. Bucket latrine	15. No facility / uses open space or field	16. Other	

4.9 If toilet is 'other' then specify

	TOILETOTH

4.10 What is the religion of the head of the household?

					HHRELIG
11. Christian	12. Muslim	14. None	15. Traditional African	16. Other	

4.11 If religion is 'other' then specify

	RELIGOTH

4.12 What ethnic group does your household belong to?

				GH_ETHNIC
11. Akan: e.g. Bono, Ashanti, Fanti.etc.	12. Bimoda, Chokosi	13. Dagarti, Frafra, Kusasi	14. Fulani	
15. Ga, Adangbe, Ewe	16. Gonja, Dagomba, Mamprusi	17. Konkomba, Basare	18. Mo	
19. Sisala, Wala	20. Zambraba	21. Banda/Pantra	22. Other, specify:	

4.13 What type of fuel does your household mainly use for cooking?

11. Electricity	12. LPG/Natural	13. Kerosene	14. Coal/Lignite	15. Charcoal	16. Wood	FUELCOOK
17. Straw/shrub/	18. Agricultural	19. Dung cakes	20. Biogas	21. Other		

4.14 If cooking fuel is 'other' then specify

	FUELOTH

4.15 In the household, is food cooked inside or outside?	11 Inside	12. Outside	13. Other, specify:	PLCCOOK

4.16 Do you have a separate room which is used as a kitchen? ……	1. Yes	2. No	KITCHEN
4.17 How many rooms are there in your household including kitchen? ……			ROOMS
4.18 How many persons slept in the household last night? ……			PERSONS

4.19 Do you own or rent the house you live in, or do you have another type of arrangement, such as "perching"?

11. Sole Ownership	12. Joint Ownership	13. Renting	14. Family/relative's house	OWNHOUSE
15. House provided rent free	16. Perching	17. Other:	88. NK	

4.20 Does household have: ……..			
4.20.1 Electricity?	1. Yes	2. No	GH_ELECTR
4.20.2 Chickens? ……	1. Yes	2. No	GH_CHICKEN
4.20.3 Sheep?	1. Yes	2. No	GH_SHEEP
4.20.4 Other animals? …….	1. Yes	2. No	GH_OTHANIMAL
4.20.5 Mattress?	1. Yes	2. No	GH_MATTRESS
4.20.6 Stove or cooker?	1. Yes	2. No	GH_PRESCOOK
4.20.7 Chair?	1. Yes	2. No	GH_CHAIR
4.20.8 Cot or bed?	1. Yes	2. No	GH_BED
4.20.9 Divider?	1. Yes	2. No	GH_DIVIDER
4.20.10 Table?	1. Yes	2. No	GH_TABLE
4.20.11 Electric fan?	1. Yes	2. No	GH_FAN
4.20.12 Radio or transistor?	1. Yes	2. No	GH_RADIO
4.20.13 Television?	1. Yes	2. No	GH_BWTV
4.20.14 Sewing machine?	1. Yes	2. No	GH_SEW
4.20.15 Mobile telephone?	1. Yes	2. No	GH_MOBILE
4.20.16 Mosquito net? ……	1. Yes	2. No	GH_MOSNET
4.20.17 Computer?	1. Yes	2. No	GH_COMP
4.20.18 Refrigerator?	1. Yes	2. No	GH_FRIDGE
4.20.19 Watch or clock?	1. Yes	2. No	GH_WATCH
4.20.20 Bicycle? ……	1. Yes	2. No	GH_BICYCLE
4.20.21 Motorcycle or scooter?	1. Yes	2. No	GH_MOTOCY
4.20.22 Animal-drawn cart?	1. Yes	2. No	GH_ANIMCART
4.20.23 Car? ……	1. Yes	2. No	GH_CAR
4.20.24 Thresher?	1. Yes	2. No	GH_THRSHR
4.20.25 Tractor? ……....	1. Yes	2. No	GH_TRACTOR

4.21 Does this household own any land? …….……..	1. Yes	2. No	OWNLAND

5. MOTHER'S DIET

Did the mother consume any of the following in the last seven days?

5.1 Any kind of redmeat (eg goat)	11. Never	12. Once /w	13. Twice-Four/w	14. Five-six/w	15. Daily	REDM
5.2 Any kind of poultry (eg chicken)	11. Never	12. Once /w	13. Twice-Four/w	14. Five-six/w	15. Daily	WHITE
5.3 Any kind of liver…….	11. Never	12. Once /w	13. Twice-Four/w	14. Five-six/w	15. Daily	LIVER
5.4 Any kind of fish (fresh or dried)	11. Never	12. Once /w	13. Twice-Four/w	14. Five-six/w	15. Daily	FISH
5.5 Egg……	11. Never	12. Once /w	13. Twice-Four/w	14. Five-six/w	15. Daily	EGG
5.6 Milk……	11. Never	12. Once /w	13. Twice-Four/w	14. Five-six/w	15. Daily	MILK
5.7 Yoghurt/curd/buttermilk……..	11. Never	12. Once /w	13. Twice-Four/w	14. Five-six/w	15. Daily	YOGH
5.8 Butter / milk cream……..	11. Never	12. Once /w	13. Twice-Four/w	14. Five-six/w	15. Daily	BUTTE
5.9 Peanuts…….	11. Never	12. Once /w	13. Twice-Four/w	14. Five-six/w	15. Daily	PEANU
5.10 Vegetable oil…….	11. Never	12. Once /w	13. Twice-Four/w	14. Five-six/w	15. Daily	VEGO
5.11 Carrots……...	11. Never	12. Once /w	13. Twice-Four/w	14. Five-six/w	15. Daily	CARRO
5.12 Tomatoes (red)……	11. Never	12. Once /w	13. Twice-Four/w	14. Five-six/w	15. Daily	TOMA
5.13 Pumpkin (yellow)……..	11. Never	12. Once /w	13. Twice-Four/w	14. Five-six/w	15. Daily	PUMP
5.14 Dark green leafy vegetables…	11. Never	12. Once /w	13. Twice-Four/w	14. Five-six/w	15. Daily	LEAFV
5.15 Beans/peas……	11. Never	12. Once /w	13. Twice-Four/w	14. Five-six/w	15. Daily	PEAS
5.16 Papaya (yellow)…….	11. Never	12. Once /w	13. Twice-Four/w	14. Five-six/w	15. Daily	PAPAY
5.17 Jackfruit (yellow)…….	11. Never	12. Once /w	13. Twice-Four/w	14. Five-six/w	15. Daily	JACK
5.18 Mango (yellow)…….	11. Never	12. Once /w	13. Twice-Four/w	14. Five-six/w	15. Daily	MANG
5.19 Banana…….	11. Never	12. Once /w	13. Twice-Four/w	14. Five-six/w	15. Daily	BANA
5.20 Orange……...	11. Never	12. Once /w	13. Twice-Four/w	14. Five-six/w	15. Daily	ORAN
5.21 Watermelon…….	11. Never	12. Once /w	13. Twice-Four/w	14. Five-six/w	15. Daily	WMEL
5.22 Melon (yellow)…….	11. Never	12. Once /w	13. Twice-Four/w	14. Five-six/w	15. Daily	MELO
5.23 Guava……..	11. Never	12. Once /w	13. Twice-Four/w	14. Five-six/w	15. Daily	GUAV
5.24 Red palm oil……	11. Never	12. Once /w	13. Twice-Four/w	14. Five-six/w	15. Daily	RPOIL
5.25 Plantain ……..	11. Never	12. Once /w	13. Twice-Four/w	14. Five-six/w	15. Daily	PLANT

6. MATERIALS USED IN THE CONSTRUCTION OF THE HOUSE [OBSERVE]

6.1 Floor of sleeping room	11. Cement	12. Mud/clay	14. Tiled	13. Other:	88. NK	FLOOR
6.2 Roofing ……...	11. Metal	12. Asbestos	13. Thatch	14. Mud	15. Other:	ROOF
6.3 Wall …….	11. Cement	12. Mud	13. Other:			WALL

END OF BASELINE FORM, PLEASE THANK THE RESPONDENT AND CHECK YOUR FORM

KINTAMPO HEALTH RESEARCH CENTRE NEOVITA TRIAL **INFANT FORM** 25 JANUARY 2011, v2.0	**INF Form No.**	FORMNO

1. BACKGROUND and ID

1.1 Ncluster …….…….…….. NCLUSTR

1.2 Compound no..... COMPNO

1.3 Woman's name.……..... WOMNAM

1.4 Woman's Neovitaid.…….. WOMANI

1.5 Infant's name.……..... INFNAME

1.6 Infant's Neovitaid.…….…….. SUBJECT

1.7 Visit number……..……... VAGE

1.8 Date of visit (dd/mm/yyyy)…….…… DATEVIS

1.9 Staff code ……...……..…….. FW

2. STATUS

2.1 Mother status at time of visit:

11. Present	12. Currently in hospital	13. Temporarily absent (for another reason)	14. Died	WSTATU
15. Moved out	16. Refused	17.Withdrawn	99. NA	

2.2 Infant's status at time of visit:

11. Present	12. Currently in hospital	13. Temporarily absent (for another reason)	14. Died	ISTATUS
15. Moved out	16. Refused	17.Withdrawn	99. NA	

2.3 If died, date of death: (dd/mm/yyyy) …..……
[DRAW A LINE THROUGH IF NA] DATEDIE

2.4 If the baby or mother has moved out (ie Q2.3 = 15) then where has the baby or mother moved?

11. Another compound in study area	12. A compound outside the study area	88. NK	99.NA	MOVET

2.4.1 Village/town name VILLNMT

2.4.2 Village/town code (NA=999 or outside SA, NK=888)…… VILLCMT

2.4.3 Please provide compound no…
(NA or outside SA = 99999999;NK = 888888888) COMPMT

2.5 Who is the respondent for this interview?

11. Mother	12. Father	13. Other family member	14. Other guardian / Caretaker	15. No card / no respondent	INFORMA

IF MOTHER AWAY USE ANOTHER RESPONDENT. BUT MUST HAVE INFANT'S NEOVITA ID CARD.

2.6 Is the interview being conducted by phone? …… 1. Yes | 2. No PHONE

STOP IF NO RESPONDENT OR THE INFANT NOT PRESENT; PUT A DOUBLE LINE ACROSS REST OF FORM.

3. INFANT FEEDING OVER LAST 24 HOURS

3.1	In the last 24 hours, did you breastfeed or put baby to the breast? …….	1. Yes	2. No	8. NK

BREASTN

3.2 In the last 24 hours, was the baby offered anything else [PROMPT]:

3.2.1	Breast milk from another mother? ……	1. Yes	2. No	8. NK	WETNUR
3.2.2	Any other milk other than breast milk such as tinned, powdered, or fresh animal milk or commercially produced infant formula?.....	1. Yes	2. No	8. NK	OTHMILI
3.2.3	Water ……	1. Yes	2. No	8. NK	WATER
3.2.4	Medicines, vitamins or ORS ……	1. Yes	2. No	8. NK	MEDICIN
3.2.5	Other water based fluids [PROMPT for: juice, tea, sugar, glucose, traditional medicines]? ……	1. Yes	2. No	8. NK	OTHFLUI
3.2.6	Any foods [PROMPT for: any solid foods, porridge, bread, rice, cerelac, nutrimix]? ……...	1. Yes	2. No	8. NK	SOLID

4. IMMUNISATIONS

4.1 Has the child been vaccinated since the last visit? ……	1. Yes	2. No	8. NK	VACC

IF NO, THEN PUT A DOUBLE LINE THROUGH THIS SECTION 4.2 AND MOVE TO SECTION 4.4

SELF REPORT OF IMMUNISATION

4.2 What type of immunisations did the child receive?

4.2.1 Oral medicine given by mouth? ……	1. Yes	2. No	8. NK	RORAL
4.2.2 Injection into leg? ……..……	1. Yes	2. No	8. NK	RLEG
4.2.3 Injection into arm? ……...……	1. Yes	2. No	8. NK	RARM

4.3 What was the name of the vaccination (s)?

4.3.1 Polio? ……...……	1. Yes	2. No	8. NK	RPOLIO
4.3.2 BCG? ……...……	1. Yes	2. No	8. NK	RBCG
4.3.3 DTP/Penta? …….	1. Yes	2. No	8. NK	RPENTA
4.3.4 Measles? ……..……	1. Yes	2. No	8. NK	RMEAS
4.3.5 Yellow fever? ……	1. Yes	2. No	8. NK	RYELLO

4.4 Is there a BCG scar? (OBSERVE BOTH UPPER ARMS).....	1. Yes	2. No	8. NK	9. NA	BCGS

NOW ASK FOR WRITTEN RECORD OF VACCINATION
(PROMPT FOR ANC, Family planning, or child health records or any other written record of vaccination)

4.5 Written vaccination record viewed? ……	1. Yes	2. No	VACCCA

IF NO PUT A DOUBLE LINE THROUGH THIS SECTION AND MOVE TO SECTION 5

TRANSCRIBE INFORMATION DIRECTLY FROM CARD ONTO THIS FORM
09090909=Did not receive, 08080808=Received but date not known

Tuberculosis (BCG)

4.6. BCG birth dose date received ……..……									DATEBC

Poliomyelitis (Polio)

4.7.1 Polio birth dose date received ……..……									DATEPO
4.7. 2 Polio1 dose date received ……..……..……									DATEPO
4.7.3 Polio2 dose date received ……..……									DATEPO
4.7.4 Polio3 dose date received ……..……									DATEPO

Diptheria/Tetanus/Pertussis/Hepatitis B/Hib (Penta)

4.8.1 DTP1-HepB-Hib (penta) 1 dose date received….									DATEPE
4.8.2 DTP2-HepB-Hib (penta) 2 dose date received...									DATEPE
4.8.3 DTP3-HepB-Hib (penta) 3 dose date received…									DATEPE

Measles

4.9. 1 Measles dose date received ……									DATEME

Yellow fever

4.10.1 Yellow fever dose date received…… | | | | | | | | |

5. VITAMIN A SUPPLEMENTATION

5.1 Have you or your child received vitamin A supplementation since the last visit?

1. Child received	2. Mother received	3. Both child and mother received	4. Neither	8. NK	VITA

IF NEITHER OR NK DRAW A DOUBLE LINE THROUGH THIS SECTION AND GO TO SECTION 6

NOW ASK FOR WRITTEN RECORD OF MOTHER'S AND CHILD'S VITAMIN A SUPPLEMENTATION

(PROMPT FOR ANC, Family planning, or child health records or any other written record of supplementation)

Maternal vitamin A supplementation

5.2.1 Maternal vitamin A record viewed? (9.NA, not received)…….	1. Yes	2. No	9. NA	VITACAR
5.2.2 Maternal vitamin A dose date received…… 09090909=Did not receive; Did not view record. 08080808=Received but date not recorded on record.				DATEVIT

Infant vitamin A supplementation

5.3.1 Infant vitamin A record viewed? (9.NA, not received)…….	1. Yes	2. No	9. NA	VITACAR
5.3.2 Infant vitamin A dose 1 date received…… 09090909=Did not receive; Did not view record. 08080808=Received but date not recorded on record.				DATEVIT
5.3.3 Infant vitamin A dose 2 date received…… 09090909=Did not receive; Did not view record. 08080808=Received but date not recorded on record.				DATEVIT

6. HEALTH CARE SINCE LAST VISIT

6.1.1 Have you had contact with a health care provider or health facility for this child since the last visit? [PROMPT FOR OUTREACH CLINIC, IMMUNISATIONS, ILLNESS]……	1. Yes	2. No	8. NK	CONTAC
6.1.2 Has the child been unwell with an illness or injury since the last visit?	1. Yes	2. No	8. NK	UNWELL

IF NO / NK PUT A DOUBLE LINE THROUGH THIS SECTION AND GO TO SECTION 7

6.1.3 If yes how many different illnesses/injuries……. | | UNWELL

6.2. FIRST ILLNESS/INJURY

6.2.1 Date illness/injury started (dd/mm/yyyy)…….. [IF NK or ONGOING THEN PUT 08080808]				STDATE1
6.2.2 Date illness/injury ended (dd/mm/yyyy)…… [IF NK or ONGOING THEN PUT 08080808]				ENDDAT
6.2.3 Is the illness ongoing?	1. Yes	2. No	8. NK	ONGOIN
6.2.3 Was care sought outside the home while the child had this illness/injury?.....	1. Yes	2. No	8. NK	CARESE
6.2.4 Was the child admitted to sleep at least one night in a health facility during this illness/injury?.....	1. Yes	2 No	8. NK	ADM1

IF NO DRAW A DOUBLE LINE THROUGH SECTION AND GO TO SECTION 6.3.
IF THERE IS <u>NO SECOND ILLNESS</u> THEN DRAW A DOUBLE LINE THROUGH SECTION AND GO TO SECTION 7.

6.2.5 How many facilities?.....		SEEKCAI
6.2.6 Facility 1 code		FCODE11
6.2.7 Facility 2 code		FCODE21
6.2.8 Facility 3 code		FCODE31

6.2.9 What was the reason for the admission?

Acute lower respiratory tract infection / pneumonia ……	1. Yes	2. No	8. NK	ALRI1
Diarrhea ……	1. Yes	2. No	8. NK	DIARRHE

Fever/malaria …….….	1. Yes	2. No	8. NK	FEVMAL
Injury ……..……	1. Yes	2. No	8. NK	INJURY1
Others ……	1. Yes	2. No	8. NK	OTHERS
If other, specify ……..				HOSOTH

IF NO SECOND ILLNESS THEN PUT A DOUBLE LINE THROUGH THIS SECTION AND GO TO SECTION 7

6.3. SECOND ILLNESS/INJURY

6.3.1 Date illness/injury started (dd/mm/yyyy)……... [IF NK or ONGOING THEN PUT 08080808]				STDATE2
6.3.2 Date illness/injury ended (dd/mm/yyyy)…… [IF NK or ONGOING THEN PUT 08080808]				ENDDAT
6.3.3 Is the illness ongoing?	1. Yes	2. No	8. NK	ONGOIN
6.3.3 Was care sought outside the home while the child had this illness/injury?.....	1. Yes	2. No	8. NK	CARESE
6.3.4 Was the child admitted to sleep at least one night in a health facility during this illness/injury?.....	1. Yes	2 No	8. NK	ADM2

IF NO EITHER DRAW DOUBLE LINE THROUGH SECTION AND GO TO SECTION 7.

6.3.5 How many facilities?.....		SEEKCA
6.3.6 Facility 1 code		FCODE12
6.3.7 Facility 2 code		FCODE22
6.3.8 Facility 3 code		FCODE32

6.39 What was the reason for the admission?

Acute lower respiratory tract infection / pneumonia …….……	1. Yes	2. No	8. NK	ALRI1
Diarrhea ……..……..……..……	1. Yes	2. No	8. NK	DIARRH
Fever/malaria …….….	1. Yes	2. No	8. NK	FEVMAL
Injury ……..……	1. Yes	2. No	8. NK	INJURY1
Others ……	1. Yes	2. No	8. NK	OTHERS
If other, specify ……..				HOSOTH

7. FOLLOW UP INFORMATION
PLEASE INFORM THE MOTHER THAT THE BABY WILL HAVE A FOLLOW UP INFANT VISIT IN ONE MONTH.

7.1 Where will the baby be at the next visit?	11. This compound	12. Other compound	LOCATIO

IF THIS COMPOUND THEN END HERE AND DRAW A DOUBLE LINE THROUGH THE REST OF THE FORM

7.2 Village/town name		HOUSEID
7.3 Village/town code (NK = 888;N A or outside SA = 999) ……		VILLCOD
7.4 If another compound please provide no. (NK = 88888888; NA or outside SA = 99999999)……..		ANCOMP

7.5 PLEASE PROVIDE FULL DETAILS ABOUT HOW TO LOCATE THE BABY FOR THE NEXT VISIT

END OF INFANT FORM, PLEASE THANK THE RESPONDENT AND CHECK YOUR FORM

KINTAMPO HEALTH RESEARCH CENTRE COHORT / NEOVITA PROJECT INFANT VPM FORM (18 Sept 2012, v1.0 ENGLISH)	INFANT VPM Form No.	FORMNO

BACKGROUND and ID:

PLEASE VERIFY ALL THE INFORMATION ON THE PRINTED LABEL BELOW. START BY ASKING FOR THE MOTHER'S NEOVITA ID CARD. IF THE NEOVITA CARD IS MISSING, PLEASE ASK TO EXAMINE THE ANC CARD, THE CHILD HEALTH RECORD, or ANY OTHER SOURCE THAT MAY HAVE THE INFORMATION. IF ANY OF THE INFORMATION IS INCORRECT, PLEASE CORRECT IT.

1.1. Ncluster…….. NCLUSTER

1.2. Woman's ID……. WOMANID

1.3. Woman's name…….. WOMNAME

1.4. Infant ID number…..... SUBJECTID

1.5. Date of delivery [080808 = NK]……... DATEDELIV

1.5.1 Time of delivery [24-hr clock;8888 = NK] TIMEDELIV

1.6. Date of death [080808 = NK]……... DATEDIED

CONFIRM THE DATE OF DEATH LISTED ON THE LABEL. IF CONFIRM A DIFFERENT DATE, DOUBLE LINE THROUGH DATE ON LABEL AND RECORD CONFIRMED DATE.

1.6.1 Did the infant die during the rainy season or the dry season?..... SEASON

1. Rainy	2. Dry	8. NK

1.6.2. IF DATE OF DEATH IS NK (08080808), then ask the woman: how soon after birth did the baby die? AGED

1. Within 24 hours of birth	2. 1-13 days	3. 2-3 weeks		4. 4-7 weeks
5. 2-3 months	6. 4-5 months	7. 6-11 months	8. NK	9. NA, date known

1.7. PLACE THE INFANT IN ONE OF THE FOLLOWING GROUPS. CONFIRM THIS WITH THE RESPONDENT DURING THE INTERVIEW. CLASSIF

1. Stillbirth = Born dead / child did not cry or move or breathe after birth after 22w gestation	2. Early neonatal death = Live birth with age at death 0 to 6 days
3. Late neonatal death = Live birth with age at death 7-27 days	4. Postneonatal death = Live birth with age at death 28 days or more

1.8. Did you verify the WOMAN'S ID on the label? VERIFY

1. Yes, verified with Neovita card.	2. Yes, verified without Neovita card.	3. No, Neovita card lost and no other source to verify.

1.9. Date of interview: ……..... DATEVISIT

1.10. Staff code: …….....……. FW

1.11. Time interview began. 24 hour clock…….…..... TIMEBEG

1.12. Time interview finished. 24 hour clock …….....…. TIMEFIN

2. INFORMATION ABOUT THE RESPONDENT

ASK TO SPEAK TO THE MOTHER OR TO ANOTHER ADULT CARETAKER WHO WAS PRESENT DURING THE ILLNESS THAT LED TO THE INFANT'S DEATH IF THIS IS NOT POSSIBLE, ARRANGE A TIME TO VISIT THE HOUSEHOLD WHEN THE MOTHER OR CARETAKER WILL BE HOME.

2.1. IS A RESPONDENT AVAILABLE? ..... RESPOND

1. Yes	2. No

2.2. CONSENT GIVEN FOR VERBAL AUTOPSY?..... VPMCONS

1. Yes	2. No	9. NA no respondent

IF RESPONDENT DOES NOT GIVE CONSENT, OR THERE IS NO RESPONDENT, PLEASE TRY TO FIND ANOTHER RESPONDENT. IF NECESSARY PLEASE RETURN TO THE COMPOUND AT ANOTHER TIME TO FIND A RESPONDENT AND COMPLETE THE INTERVIEW. IF THERE WILL NEVER BE A RESPONDENT, PLEASE SUBMIT AS PROBLEM FORM.

2.3. RESPONDENT'S NAME: RESPNAME

2.4. RESPONDENT'S AGE…… RESPAGE

2.5. WHAT IS THE RELATIONSHIP OF THE MAIN RESPONDENT TO THE DECEASED CHILD? RELATION

11. Mother	12. Father	13. Grandmother	14. Grandfather	15. Aunt	16. Uncle
17. TBA	18. Other male: _____		19. Other female : _____		

2.6. Did the respondent live with the deceased child in the period leading to her/his death? 1. Yes 2. No RESLIVE

2.7. TOTAL NUMBER PRESENT WHO PARTICIPATED AT INTERVIEW (EXCLUDING INTERVIEWER[S])? ..... TOTINT

2.8. OF THOSE PARTICIPATING IN THE INTERVIEW, WERE THE FOLLOWING PERSONS PRESENT AT THE ILLNESS THAT LED TO STILLBIRTH, DEATH OR HOSPITALISATION?

2.8.1. The infant's mother…….	1. Yes	2 No
2.8.2. The infant's father ……	1. Yes	2 No
2.8.3. The infant's grandmother ……..	1. Yes	2 No
2.8.4. The infant's grandfather…….	1. Yes	2 No
2.8.5. The infant's aunt……	1. Yes	2 No
2.8.6. The infant's uncle……	1. Yes	2 No
2.8.7. TBA……	1. Yes	2 No
2.8.8. Other, SPECIFY:_____	1. Yes	2 No

PRESDEATH1 PRESDEATH2 PRESDEATH3 PRESDEATH4 PRESDEATH5 PRESDEATH6 PRESDEATH7 PRESDEATH8

2.9. IF THE RESPONDENT IS NOT THE MOTHER, GIVE THE REASON WHY: RESPMO

1. Mother is not resident compound member	2. Mother is not present	3. Mother is dead	4. Mother is not capable of answering	5. Mother refused
6. Other:		8. NK	9. NA, mother is informant	

2.10. How is the mother's health now? MHEALT

1. Healthy	2. Ill	3. Not alive	8. NK	9. Not applicable

2.11. IF THE MOTHER IS DEAD:

2.11.1. HOW MANY DAYS AFTER DELIVERY DID SHE DIE? MODIED
[888 NK, 999 NA / DID NOT DIE, 000 if less than 24 hours or died during delivery]

2.11.2. HOW MANY MONTHS AFTER DELIVERY DID SHE DIE? MODIEDMTH
[0 – 12; 88 = NK, 99 = NA / DID NOT DIE]

IF THE RESPONDENT IS THE MOTHER, SKIP QUESTIONS 2.12 AND 2.13 AND CONTINUE FROM SECTION 3

2.12. If the respondent is not the mother, how old is the respondent? R_AGE
[88=NK; 99 = NA; respondent is mother].....

2.13. What is the highest level of schooling or educational attainment *you the respondent* have attained? RESEDUL

11. None	12. Primary school	13. Middle, continuation school, JSS	14. Technical, commercial, SSS, Secondary school	
15. Post-middle college, secretarial	16. Post secondary, nursing, polytechnic	17. University	88. NK	99. NA, respondent is mother

3. INFORMATION ABOUT THE MOTHER

3.1 How old is the mother? (IN YEARS; 88=NK)…..…… | | | MAGE

3.2. What is the mother's nationality / citizenship?

1. Ghanaian	2. Other (SPECIFY):	NATION

3.3. To what ethnic group does the mother belong?

11. Akan: e.g. Bono, Ashanti, Fanti.etc.	12. Bimoda, Chokosi	13. Dagarti, Frafra, Kusasi	14. Fulani	GH_ETHNIC
15. Ga, Adangbe, Ewe	16. Gonja, Dagomba, Mamprusi	17. Konkomba,asare	18. Mo	
19. Sisala, Wala	20. Zambraba	21. Banda/Pantra	22. Other, SPECIFY:	

3.4. Is the mother normally resident in the study area ?..... | 1. Yes | 2. No | 8. NK | RESIDENCE

3.5. How many years of schooling did the mother have? [00=None, 88=NK]..... | | | EDUWOMAN

3.6. What was the mother's highest level of schooling (or educational attainment)?

11. None	12. Primary school	13. Middle,continuation school, JSS	14. Technical, commercial, SSS, Secondary school	EDUCLEVEL
15. Post-middle college, secretarial	16. Post secondary, nursing, polytechnic	17. University	88. NK	

3.7. Was the mother able to read or write? ..... | 1. Yes | 2. No | 8. NK | READWRITE

3.8. What was the mother's main economic activity status in the year prior to the baby's death?

11. Mainly employed	12. Mainly unemployed	14. Home maker	15. Student		OCCWOMAN
16. Pensioner	17. Does not work	18. Other	88. NK	99. NA	

If occupation of woman was 'other' then specify

	MOCCOTH

3.9. What was the mother's marital status?

				MARRIED
11. Never married / single	12. Married	13. Cohabiting		
14. Separated	15. Divorced	16. Widowed	88. NK	

4. INFORMATION ABOUT THE CHILD

4.1. Was the child a singleton or multiple birth? ..... | 1. Singleton | 2. Multiple | MULTIPLE

[IF TWO OR MORE CHILDREN ARE BORN, IT IS COUNTED AS A MULTIPLE BIRTH, EVEN IF ANY BABY IS BORN DEAD. IF MULTIPLE BIRTH THEN FILL A FORM FOR EACH BABY WHO DIES.]

4.2. If multiple, was this the first, second, or later in birth order?

1. First	2. Second	3. Third or more	8. NK	9. Not applicable/singleton birth	BORDER

4.3. Was the baby male or female?..... | 1. Male | 2 Female | 8. NK | SEX

4.4. What was the child's name?
[Stillbirth = NA, FOR LIVE BIRTH USE DAY NAME IF NO OTHER NAME IS AVAILABLE]

	CNAME

4.5. For how long was the child ill before s/he died?
[in days, 888 = NK, 000 = died during delivery]..... | | | | DURILL

4.6. Did the baby die suddenly?..... | 1. Yes | 2 No | 8. NK | DIESUDD

5. OPEN HISTORY QUESTIONS

5.1. Story of the illness

ALLOW THE RESPONDENT TO TELL YOU ABOUT THE PREGNANCY, DELIVERY AND THE BABY'S INJURY OR ILLNESS IN HER OWN WORDS. WRITE DOWN WHAT THE RESPONDENT TELLS YOU IN HER OWN WORDS. DO NOT PROMPT EXCEPT FOR ASKING WHETHER THERE WAS ANYTHING ELSE AFTER THE RESPONDENT FINISHES. KEEP PROMPTING UNTIL THE RESPONDENT SAYS THERE WAS NOTHING ELSE. WHILE RECORDING, UNDERLINE ANY UNFAMILIAR TERMS.
ALSO REMEMBER TO PROMPT ABOUT CARESEEKING DURING PREGNANCY, LABOUR, DELIVERY, AFTER THE BIRTH OF THE CHILD AND DURING THE FATAL ILLNESS. ASK WHAT THE MOTHER DID AND WHO SHE SOUGHT CARE FROM DURING ALL OF THESE TIMES.

FIRST ASK "Could you tell me about the pregnancy for this child"?

THEN ASK "Could you tell me about the labour and delivery for this child"?

THEN ASK “Could you tell me what the baby was like at birth”?

THEN ASK “Could you tell me about what happened to the child immediately after delivery”? [IN THIS QUESTION WE WANT TO KNOW WHAT HAPPENED TO THE BABY IMMEDIATELY AFTER DELIVERY. THAT IS IF THE BABY NEEDED ANY TREATMENT OR SPECIAL CARE AS SOON AS HE/SHE WAS BORN.’]

THEN FOR LIVE BIRTHS ONLY ASK "Could you tell me about the child's illness or accident that led to death?" [IF STILLBIRTH PUT A DOUBLE LINE THROUGH THIS SECTION]

5.2 Cause of death

NOW PLEASE ASK THE RESPONDENT "What do you think was the cause of death?

5.2.1 Cause of death 1		COD1
5.2.2 Cause of death 2		COD2

6. DETAILS OF PREGNANCY, LABOUR AND DELIVERY

COMPLETE THIS SECTION FOR ALL INFANTS

PLEASE TELL THE RESPONDENT THAT YOU WOULD LIKE TO ASK SOME QUESTIONS CONCERNING THE MOTHER AND SYMPTOMS THAT THE DECEASED HAD/SHOWED AT BIRTH AND SHORTLY AFTER. PLEASE SAY THAT SOME OF THESE QUESTIONS MAY NOT APPEAR TO BE DIRECTLY RELATED TO THE BABY'S DEATH BUT ASK THE RESPONDENT TO PLEASE BEAR WITH YOU AND ANSWER ALL THE QUESTIONS. THEY WILL HELP US TO GET A CLEAR PICTURE OF ALL POSSIBLE SYMPTOMS THAT THE DECEASED HAD.

6.1. Pregnancy

6.1.1. How many births including stillbirths did the mother have before this baby?

1. None	2. One	3. Two	4. Three	5. Four	6. Five or more	8. NK	PARITY

6.1.2. Did the mother receive vaccinations since reaching adulthood including during this pregnancy?.....	1. Yes	2. No	8. NK	VACCINATEF

6.1.3. How many doses of vaccine?...	1. One	2. Two	3. Three	4. Four	5. Five or more	8. NK	VACCINDOSE

6.1.4. Did the mother receive tetanus toxoid during this pregnancy?.....	1. Yes	2. No	8. NK	TTOXOID

6.1.5. How many tetanus toxoid immunisations did you receive during that pregnancy? [00 = NONE, 88 = NK, ASK TO SEE ANY MEDICAL RECORDS, YELLOW CARD]…		TETTOXD
6.1.6. How many tetanus toxoid immunisations have you ever received before that pregnancy? [00 = NONE, 88 = NK, ASK TO SEE ANY MEDICAL RECORDS, YELLOW CARD]….....		TETTOXB
6.1.7. How many times did you receive antenatal care from a doctor or nurse during that pregnancy? [00 = NONE, 88=NK, ASK TO SEE ANTENATAL CARE RECORD, EXCLUDE ILLNESS]		ANC

6.1.8. During pregnancy did the mother suffer from high blood pressure? …...	1. Yes	2. No	8. NK	HIBPPREG
6.1.8.1. Was this in the last 3 months of pregnancy?.....	1. Yes	2. No	8. NK	LATEPREGBP
6.1.9. During pregnancy did the mother suffer from excessive vaginal bleeding?.....	1. Yes	2. No	8. NK	VAGBLEED
6.1.9.1.Was this during the first 6 months of pregnancy?	1. Yes	2. No	8. NK	EARLYVAGBI
6.1.9.2.Was this during the last 3 months of pregnancy? ….....	1. Yes	2. No	8. NK	BLEED3MTHS
6.1.10. At any time during the pregnancy did the mother ever have foul smelling vaginal discharge? ….....	1. Yes	2. No	8. NK	VAGDISC
6.1.10.1.Was this during the last 3 months of pregnancy? ….....	1. Yes	2. No	8. NK	DISCHARGE
6.1.11. At any time during the pregnancy did the mother ever suffer from blurred vision? ….....	1. Yes	2. No	8. NK	BLURVIS

Did any of the following problems occur during the late part of that pregnancy (last 3 months)?

6.1.12. Diabetes?.....	1. Yes	2 No	8. NK	DIABETES
6.1.13. Asthma?.....	1. Yes	2 No	8. NK	ASTHMA
6.1.14. Epilepsy?.....	1. Yes	2 No	8. NK	EPILEPSY
6.1.15. Malnutrition?.....	1. Yes	2 No	8. NK	MALNUT
6.1.16. Obesity?.....	1. Yes	2 No	8. NK	OBESITY

6.1.17. Cancer?.....	1. Yes	2 No	8. NK	CANCER
6.1.18. Tuberculosis?.....	1. Yes	2 No	8. NK	TB
6.1.19. Sickle cell disease?.....	1. Yes	2 No	8. NK	SICKLE
6.1.20. Heart Disease?.....	1. Yes	2 No	8. NK	HEART_DIS
6.1.21. Chronic obstructive pulmonary disease?.....	1. Yes	2 No	8. NK	COPD
6.1.22. Dementia?.....	1. Yes	2 No	8. NK	DEMENTIA
6.1.23. Depression?.....	1. Yes	2 No	8. NK	DEPRESS
6.1.24. Stroke?.....	1. Yes	2 No	8. NK	STROKE
6.1.25. Arthritis?.....	1. Yes	2 No	8. NK	ARTHRITIS
6.1.26. Kidney disease?.....	1. Yes	2 No	8. NK	KIDNEY
6.1.27. Liver disease?.....	1. Yes	2 No	8. NK	LIVER
6.1.28. Any bleeding from the vagina?.....	1. Yes	2 No	8. NK	PBLEED
6.1.29. Any vaginal discharge that was abnormal or worrying (because smelly or too much)?.....	1. Yes	2 No	8. NK	PDISCHARGE
6.1.30. Health worker tested the blood and said you were short of blood?…	1. Yes	2 No	8. NK	PANAEMIA
6.1.31. Health worker said you had malaria……	1. Yes	2. No	8. NK	PMALARIA
6.1.32. Health worker said you had jaundice……..	1. Yes	2 No	8. NK	PJAUNDICE
6.1.33. Severe or persistent abdominal or back pain that was not labour pain…	1. Yes	2 No	8. NK	PLONGPAIN
6.1.34. Health worker said you had diabetes ……..……	1. Yes	2 No	8. NK	PDIABETES
6.1.35. Positive syphilis test……	1. Yes	2 No	8. NK	PSYPHILIS
6.1.36. Genital ulcer……..	1. Yes	2 No	8. NK	PULCER
6.1.37. Hand or facial swelling, or rapid leg swelling…….……	1. Yes	2 No	8. NK	PFACE
6.1.39. Blurring of vision and severe headache…….……..	1. Yes	2 No	8. NK	PBLUREYE
6.1.40. Severe headache?.....	1. Yes	2 No	8. NK	HEADACHE
6.1.41. Health worker measured the blood pressure and told you it was high…	1. Yes	2 No	8. NK	PHIGHBP
6.1.42. Convulsions like in children……	1. Yes	2 No	8. NK	PCONVULSE
6.1.43. “Anidane”……	1. Yes	2 No	8. NK	PANIDANE
6.1.44. Afam /Atare? ……..……	1. Yes	2 No	8. NK	PAFAM
6.1.45. Pallor and shortness of breath (both present)……..……..…….……	1. Yes	2. No	8. NK	PALLOR
6.1.46. Puffy face….....	1. Yes	2 No	8. NK	PUFFY
6.1.47. Other:…….	1. Yes	2. No	8. NK	POTHER
6.1.47.1. If other, please specify[NA=DOUBLE LINE]				OTHERSP_ILL

6.2. Labour and delivery

6.2.1. Was the baby born more than one month early?.....		1. Yes	2 No	8. NK	PREMATURE
6.2.2. Did this child’s pregnancy end early on time or late?	1. Early	2.On time	3. Late	8. NK	PREMBAB

6.2.3. How many months pregnant were you when the baby was born? [88 = NK]				GESTATE
6.2.4. Was the baby moving in the last few days before birth? [9 = NA, respondent not biological mother].....	1. Yes	2. No	8. NK	BABMOVE
6.2.5. If the baby stopped moving when did this happen?	11. Before labour started	12. During labour	88. NK / 99. NA	MOVWHEN
6.2.6. How many hours before delivery did the baby last move? [00 = baby last moved during labour or delivery; 88 = not known]……..……				LASTMOVEHI MOVDAY
6.2.7. How many days before delivery did the baby last move? [DAYS, 00 = baby last moved during labour or delivery; 88 = not known].....				MOVDAY

6.2.8. Did the waters break before labour or during labour?

1. Before labour /delivery started	2. During labour / delivery	8. NK	WATERBRK
6.2.9. Was the baby born 24 hours or more after the water broke?.....	1. Yes	2 No / 8. NK	WATERBRK24

6.2.10. How much time before labour started did the waters break?

1. Less than 4 hours	2. 4 to 23 hours	3. 24 hours or more	8. NK	9. NA, broke during labour delivery	TIMEBRK

6.2.11. What was the colour of the liquor when the waters broke?

1. Green or brown	2. Clear or normal	3. Other, SPECIFY:	8. NK	LIQUORC

6.2.12. Was the liquor foul-smelling?.....	1. Yes	2 No	8. NK	LIQUORS
6.2.13. How long did the labor pains last [88 = not known; 99 = NA, CS]…….....				LABDURATN
6.2.14. How long in hours was the labour before the baby was born ? 88 = not known; 99 = NA, C-section]……..				LABHOURS
6.2.15. Did you have problems during the delivery?.....	1. Yes	2 No	8. NK	COMPDEL
5.2.6. Was there excess bleeding on the day labour started?	1. Yes	2. No	8. NK	XSBLEED
6.2.16.1. Heavy bleeding before labour started?.....	1. Yes	2. No	8. NK	BLDB4LABOR
6.2.16.2. Heavy bleeding during labour?.....	1. Yes	2. No	8. NK	BLDDURLABO
6.2.17. Heavy bleeding after delivery…….....……	1. Yes	2. No	8. NK	DBLEED
6.2.18. Did the mother have a fever on the day labour started?	1. Yes	2. No	8. NK	DELFEVER

Did any of the following problems occur during labour or delivery? [DELIVERY INCLUDES C-SECTION]

6.2.19. Health worker measured the blood pressure and told you it was high	1. Yes	2 No	8. NK	DHIGHBP
6.2.20. Convulsions like in children……	1. Yes	2 No	8. NK	DCONVULSE
6.2.21. Fever during labour……..……	1. Yes	2 No	8. NK	DFEVER
6.2.22. Umbilical cord delivered before the baby……	1. Yes	2. No	8. NK	DPROLAPSE
6.2.23. Umbilical cord around the baby's neck……	1. Yes	2. No	8. NK	DCORDNECK
6.2.24. Did somebody put their hand inside the womb to remove the placenta?..	1. Yes	2. No	8. NK	DRETPLAC
6.2.25. Other, specify: _____	1. Yes	2. No	8. NK	DOTHER

6.2.26 Where did the birth take place?

1. Clinic/hospital	2. Private maternity home	6. Other health facility		PLACEBIR
4. On the way to the clinic/hospital	3. At home (e.g. woman's or anyone's home)	5. Other, SPECIFY:	8. NK	

6.2.27. IF THE ANSWER TO 5.2.14. IS 1, 2 or 3, STATE WHERE. [USE FACILITY KEY CODE; OTHERWISE ANSWER 99]..……			HOSPITAL

6.2.28. Was medicine given to make the labour start? …….....	1. Yes	2. No	8. NK	AUGMENT1
6.2.29. Was medicine given after labour had already started to make the labour progress more quickly?	1. Yes	2. No	8. NK	AUGMENT2

6.2.30. Was it a normal delivery through the vagina? TYPEDELIV

1. Normally through vagina	2. Baby was pulled with instrument	3. By C-section	4. Other, SPECIFY:

6.2.31. Did you know it was going to be a C-section before labour?	1. Yes	2. No	9. NA, No CS	KNOWCS

6.2.32. Who delivered the baby? WHODELIV

1. Doctor	2. Midwife or nurse	3. Trained TBA	7. Untrained TBA	6. Medical assistant
5. Self	9. Relative	4. Other, SPECIFY:		8. NK

6.2.33. Did a birth attendant listen for fetal heart sounds during labour?		1. Yes	2. No	8. NK	LISTEN
62.35. If yes then were they present? .....….....	1. Yes	2. No	8. NK	9. NA	PRESENT

6.2.36. Was the baby abnormally positioned (lying across or bottom first or 'breech') before the time of delivery?	1. Yes	2 No	8. NK	POSITIONDEL

6.2.37. Which part of the baby came out first?

1. Head	2. Bottom	4. Feet	5. Hand/arm	BPOSN
6. More than one body part (e.g. bottom and foot)		3. C-Section	8. NK	

6.3. Status of the baby at the delivery

6.3.1. At what time of the day was the baby delivered?

1. 5am-7am	2. 8am-12pm	3. 1pm-4pm	4. 5pm-8pm	5. 9pm-1am	6. 2am-4am	TIMEDAY

6.3.2. What was used to cut the umbilical cord?

1. Clinic/hospital instrument: scissors, razorblade, knife,etc	2. New razorblade/knife(not from clinic/hospital)	CORDCUT
3. Old razor blade/knife (not from clinic/hospital)	4. Other: 8. NK	

6.3.3. Was the baby born alive or dead?	1. Alive	2. Dead	8. NK	BORNALIVE
6.3.4. Did the baby ever breathe after birth?	1. Yes	2. No	8. NK	BREATHB
6.3.5. Was anything done to try to help the baby breathe at birth?	1. Yes	2. No	8. NK	BREATHAS
6.3.6. Did the baby have difficulty in breathing after birth?…..…….....….	1. Yes	2 No	8. NK	DIFFBRATBIR

6.3.7. Did the baby ever move after birth?.....	1. Yes	2. No	8. NK	MOVEB
6.3.8. Did the baby ever cry after birth?	1. Yes	2 No	8. NK	CRYB

6.3.8.1. How long after birth did the baby first breathe?

1. Within 5 min	2. Within 5-30 min	3. More than 30 min	8. NK	9. NA/Baby never breathed after birth	FIRSTB

6.3.8.2. How long after birth did the baby first cry?

1. Within 5 min	2. Within 5-30 min	3. More than 30 min	8. NK	9. NA/Baby never cried after birth	FIRSTCRY

6.3.9. How big was the baby when he/she was born? [PROMPT]

1. Tiny	2. Smaller than average	3. Average	4. Larger than most babies	5. Very big baby	8. NK	SIZE

6.3.10. RECORD BIRTHWEIGHT. [IN KILOGRAMS; 888 = NO RECORD] [ASK FOR ANC RECORD/DISCHARGE SLIP/WEIGHING CARD/HEALTH RECORD] | | . | | | BIRTHWT

6.3.11. Were there any bruises or marks of injury on the baby's body at birth?...	1. Yes	2 No	8. NK	INJURY

6.3.12. If yes then where were the marks or signs of injury or broken bones?

1. Head	2. Shoulder	3. Hips	SITEINJ
4. Face	5. Others, SPECIFY:	9. NA	

6.3.13. Were there any signs of paralysis at birth?.....	1. Yes	2. No	8. NK	BIRPARAL
6.3.14. Was the baby's body macerated (skin and tissue was soft and pulpy)?....	1. Yes	2. No	8. NK	MACER
6.3.15. Did he/she have any congenital abnormalities at delivery?	1. Yes	2. No	8. NK	ANOMALY
6.3.15.1. Was the head size very small at the time of birth?	1. Yes	2. No	8. NK	ANENC
6.3.15. 2. Was the head size very large at the time of birth?	1. Yes	2. No	8. NK	HYDRO
6.3.15.3. Was there a mass or defect on the back of the head or spine?	1. Yes	2. No	8. NK	BIFIDA
6.3.15.4. Was there any cleft lip or palate?	1. Yes	2. No	8. NK	CLEFT
6.3.15.5. Were there any (other) limb defects?	1. Yes	2. No	8. NK	DEFECT
6.3.15.6. Were there any other malformations?.....	1. Yes	2. No	8. NK	OTHMALF
6.3.15.6.1. If yes, specify.....				OTHMALFSPE

6.3.15.7. What was the colour of the baby at birth?

1. Normal	2. Pale	3. Blue	6. Other, SPECIFY:	COLBIRTH

6.3.15.8. Did the baby become unresponsive or unconscious soon after birth (within 24 hours)?.....	1. Yes	2 No	8. NK	UNCONS

7. NEONATAL AND POSTNEONATAL DEATHS – DETAILS OF FATAL ILLNESS

FOR STILLBIRTHS, PUT A DOUBLE LINE THROUGH SECTIONS 7-10 AND GO TO SECTION 11.

7.1. General

7.1.1. On the day of birth was NAME well?.....	1. Yes	2 No	8. NK	DAYWELL

7.1.2. How old was NAME at the time the fatal illness started? [ANSWER EITHER 6.1.2.1. OR 6.1.2.2]

7.1.2.1. IN DAYS [888 = NK, 999=NA, 000 = illness started at birth]				AGEILLD

OR

7.1.2.2. IN MONTHS [88 = NK, 99=NA, 00 = illness started at birth]			AGEILLM

7.1.3. How old was NAME at the time of death? [ANSWER EITHER 6.1.3.1. OR 6.1.3.2].

7.1.3.1. IN DAYS. [888 = NK, 999=NA]				AGEDIEDD

OR

7.1.3.2. IN MONTHS [88 = NK, 99=NA]			AGEDIEDM

7.1.4. Was NAME able to cry after birth?		1. Yes	2. No	8. NK	CRYNORM
7.1.5. Did NAME stop being able to cry?	1. Yes	2 No	8. NK	9. NA	CRYSTOP
7.1.6. How long did he/she stop crying last in days? (in days) [000 = less than 1 day; 888 = not known; 999 = NA, did not stop crying]….....					CRYDAYS
7.1.7. Was NAME growing normally for his/her age?.....		1. Yes	2. No	8. NK	GROW
7.1.8. Did NAME get more sicknesses or illnesses than other children in the family or in the community?		1. Yes	2. No	8. NK	SICKNESS

7.2. Feeding

7.2.1. Was the baby ever able to suckle of bottle feed with a cup or spoon?	1. Yes	2. No	8. NK		SUCKLE
7.2.2. How soon after birth did the baby suckle or bottlefeed or feed with a cup /cup and spoon? IN HOURS [888=NOT KNOWN 999=NA].....					FHOURS
IN DAYS [888=NOT KNOWN 999=NA].....					FDAYS
7.2.3. Did the baby stop suckling or bottle feeding or feeding with a cup or spoon?.....	1. Yes	2. No	8. NK	9. NA	SSUCK
7.2.4. Was the baby able to open his/her mouth at this time?.....	1. Yes	2 No	8. NK	9 NA	OPENMOUTH
7.2.5. How soon after birth did the baby stop feeding? IN HOURS [888=NOT KNOWN 999=NA].....					SHOURS
IN DAYS [888=NOT KNOWN 999=NA].....					SDAYS
7.2.6. How soon before s/he died did the baby stop feeding? IN DAYS 00 < 24 HRS; 88=NOT KNOWN 99=NA……..					TIMENOSUCK
7.2.7. Was the breastfeeding exclusive (In other words was the baby given only breast milk and nothing else except vitamins, medicines, or ORS)?	1. Yes	2. No	8. NK	9. NA	EBF
7.2.8. Was the child growing normally during the illness that led to death?	1. Yes	2. No	8. NK		GROWTH
7.2.9. Did s/he have weight loss?	1. Yes	2. No	8. NK		WTLOSS
7.2.10. For how many days did s/he have weight loss? [IN DAYS, 000 = less than 1 day; 888 = not known; 999 = NA, no weight loss].....					WTLOSSD
7.2.11. Did s/he look very thin / wasted?.....	1. Yes	2. No	8. NK		FTHIN

7.3. Breathing

7.3.1. During the illness that led to death, did NAME have a cough?	1. Yes	2. No	8. NK		COUGH
7.3.2. If NAME had a cough, was this severe?	1. Yes	2. No	8. NK	9.NA	COUGHS
7.3.2.1. Did the child vomit after coughing?	1. Yes	2. No	8. NK	9.NA	COUGHV
7.3.3 . How many days after birth did the baby start to cough? [000 = less than 1 day; 888 = not known; 999 = NA, no cough].....					COUGHD
7.3.3.1. How long did the cough last in days? (in days) [00 = less than 1 day; 88 = not known; 99 = NA, no cough].....					COUGHLEN

7.3.4. How many days before death did the baby start to cough?

1. On the same day of death	2. 1 to 3 days before death	3. 4 to 7 days before death	4. More than 1 week but within 1 month of death	5. More than 1 month before death	8. NK	9. NA	COUGHSTART

7.3.6. During the illness that led to death, did NAME have difficult breathing?	1. Yes	2. No	8. NK	DIFFBR
7.3.7. How old was NAME when the difficult breathing started? (in days) [000 = Just born or less than 1 day; 888 = not known; 999 = NA, no difficulty breathing].....				DIFFBRDAY
7.3.8. For how long before s/he died did the baby have difficulty breathing? [00 less than 24 hours; 88 NK; 99 NA].....				TIMEDYSPN
7.3.9. How long did the difficult breathing last? (in days) [00 = less than 1 day; 88 = not known; 99 = NA, no difficulty breathing].....				DIFFBRNUM
7.3.10. During the illness that led to death, did NAME have breathlessness?.....	1. Yes	2 No	8. NK	BREATHLESS
7.3.10.1 For how long did s/he have breathlessness (in days)?.....				BRLESSDURA
7.3.11. During the illness that led to death, did NAME have fast breathing?	1. Yes	2. No	8. NK	FASTBR

7.3.12. How old was NAME in days when the fast breathing started? (IN DAYS) [000 = Just born or less than 1 day; 888 = not known; 999 = NA, no fast breathing].....				FASTBRDAY
7.3.13. How long did the fast breathing last in days? (in days) [00 = less than 1 day; 88 = not known; 99 = NA, no fast breathing].....				FASTBRNUM
7.3.14. During the illness that led to death did NAME have chest indrawing?....	1. Yes	2. No	8. NK	INDRAW
7.3.14.1. For how long did s/he have chest indrawing? (IN DAYS) [000 = less than 1 day; 888 = not known; 999 = NA, no indrawing].....				COUGHIN
7.3.15. During the illness that led to death, did NAME make a whooping sound when coughing?.....	1. Yes	2 No	8. NK	WHOOP
7.3.16. During the illness that led to death, did he/she have grunting? [DEMONSTRATE].....	1. Yes	2. No	8. NK	GRUNT
7.3.17. During the illness that led to death, did his/her nostrils flare with breathing?	1. Yes	2. No	8. NK	FLARE
7.3.18. During the illness that led to death, did NAME ever stop breathing for a long time and start again? ….....……..……	1. Yes	2. No	8. NK	APNOEA
7.3.19. During the illness that led to death, did he/she have "pneumonia"?.....	1. Yes	2 No	8. NK	PNEU

7.4. Neurological problems

7.4.1. During the illness that led to death did NAME have convulsions?	1. Yes	2 No	8. NK	IFIT
7.4.1.1. How soon after birth did the convulsions start? (IN DAYS) [000 = less than 1 day; 888 = not known; 999 = NA, no convulsions].....				FITSTART
7.4.1.2. For how long in days did they have convulsions? (IN DAYS) [00 = less than 1 day; 88 = not known; 99 = NA, no fits, spasms or convulsions].....				FITDAY
7.4.1.3. Did s/he become unconscious immediately after the convulsion?.....	1. Yes	2 No	8. NK	FITCONSC
7.4.2. Did the baby become stiff and arched backwards?	1. Yes	2. No	8.NK	ARCH
7.4.3. During the illness that led to death, did he/she have a bulging fontanelle?	1. Yes	2 No	8. NK	BULGE
7.4.3.1. How soon after birth did the bulging fontanelle start? [000 = less than 1 day; 888 = not known; 999 = NA, no bulging]				BULGES
7.4.3.2. For how many days before death did s/he have the bulging? [00 = less than 1 day; 88 = not known; 99 = NA, no bulging]				BULGED
7.4.4. During the illness that led to death, did he/she have "tetanus"? ….….....	1. Yes	2 No	8. NK	TETANUS
7.4.5. During the illness that led to death, did NAME become unresponsive or unconscious?	1. Yes	2 No	8. NK	COMA
7.4.5.1. How soon after birth did NAME become unresponsive or unconscious?[000 = less than 1 day; 888 = not known; 999 = NA, no coma]				COMAS
7.4.5.2. How long was s/he unresponsive or unconscious? [00 = less than 1 day; 88 = not known; 99 = NA, no coma]				COMAL

7.4.5.3. Did the unconsciousness start suddenly quickly within a single day or slowly over many days?

1. Suddenly	2. Over a single day	3. Slowly over many days	8. NK	9. NA	COMAON

7.5. Skin problems

7.5.1. When you gave birth to the baby, how long did it take you or someone else to dry the baby?

1. Within 30 minutes of birth	2. 30 minutes or later	3. The baby was never dried	8. NK	DRY

7.5.2. When you gave birth to the baby, how long did it take you or someone else to wrap the baby?

1. Within 30 minutes of birth	2. 30 minutes or later	3. The baby was never wrapped	8. NK	WRAP

7.5.3. From the time you gave birth to the baby till it died, what did you put on the cord?

1. Nothing, left it alone	2. Hospital / clinic medicine	3. Shea butter	4. Leaves or herbs	5. Palm oil	CORDMED
6. Ground nut oil	7. Other:			8. NK	

7.5.4. During the illness that led to death, did he/she have redness of, or drainage from the umbilical cord stump?.....	1. Yes	2. No	8. NK	DRAINUMB
7.5.5. During the illness that led to death, did he/she have redness of the umbilical cord stump?.....	1. Yes	2 No	8. NK	UBMILICRED

7.5.6. If yes, did the redness of the umbilical cord stump extend on to the abdominal skin?.....	1. Yes	2 No	8. NK	9. NA	UMBILICSKINED
7.5.7. During the illness that led to death, did he/she have pus discharging from the umbilical cord stump?.....		1. Yes	2 No	8. NK	UMBILICALPU
7.5.8. Was anything applied to the umbilical cord stump after birth?		1. Yes	2. No	8. NK	APPLUMB

If yes, what was it?

7.5.8.1. Chlorhexidine?	1. Yes	2. No	8. NK	9. NA	CHLOR
7.5.8.2. Gentian violet paint/ blue paint?	1. Yes	2. No	8. NK	9. NA	BLUE
7.5.8.3. Other, specify: _____	1. Yes	2. No	8. NK	9. NA	OTHAPPL

7.5.9. During the illness that led to death, were there any of the following on the baby's skin:

Bumps containing pus?.....	1. Yes	2. No	8. NK	PUSTULE
Blisters?.....	1. Yes	2. No	8. NK	BLISTER
Single large area of pus?.....	1. Yes	2. No	8. NK	EMPYEMA
Redness with swelling?.....	1. Yes	2. No	8. NK	ERYTHEMA
Areas of skin that were hot or peeling?.....	1. Yes	2. No	8. NK	SRED
Areas of skin that turned black?.....	1. Yes	2 No	8. NK	BLACKSKIN

7.5.10. For how long did the baby have skin bumps containing pus or a single area with pus? [01 to 28, 88 NK, 99 NA].....			PUSTULEDUR

7.6. Diarrhoea and abdominal symptoms

7.6.1. During the illness that led to death did he/she have any abdominal problems?.....		1. Yes	2 No	8. NK	ABDPROB
7.6.2. During the illness that led to death did he/she have frequent loose or liquid stools?		1. Yes	2. No	8. NK	STOOLS
7.6.3. During the illness that led to death did he/she have "diarrhoea"?.....		1. Yes	2 No	8. NK	DIARR
7.6.4. How long before death did the loose or liquid stools start? (IN DAYS) [00 = less than 1 day; 88 = not known; 99 = NA, no loose or liquid stools]……					DIARRSTART
7.6.5. How long did NAME have loose or liquid stools in days? (IN DAYS) [000 = less than 1 day; 888 = not known; 999 = NA, no loose or liquid stools]..					DIARRDAY
7.6.6. How many stools did he/she have on the day that the diarrhoea / loose or liquid stools was most frequent? (IN DAYS) [88 = Not known, 99 = NA / Did not have diarrhoea]					NUMDIARR
7.6.7. Do you feel that this represented more loose or liquid stools than usual for the child? [9 = NA / Did not have diarrhoea].....	1. Yes	2. No	8. NK	9. NA	DIARRNORM
7.6.8. During the illness that led to death, was there visible blood in the loose or liquid stools? [9 = NA / Did not have diarrhoea].....	1. Yes	2 No	8. NK	9. NA	BLDIARR
7.6.9. During the illness that led to death, did he/she have swelling/distension of the abdomen?		1. Yes	2. No	8. NK	SWABDO
7.6.10. How many days after birth did the baby start to have swelling of the abdomen? [000=less than 1 day; 888=not known; 999=NA, no swelling].....					SWABDOD
7.6.11. For how long did s/he have swelling of the abdomen? [00 = less than 1 day; 88 = not known; 99 = NA, no swelling].....					SWABDOL
7.6.12. Did the swelling develop rapidly within days or gradually over months?	1. Rapidly over days	2. Slowly over months	8.NK	9.NA	SWABDOR
7.6.13. Did s/he have a mass in the abdomen?		1. Yes	2. No	8. NK	MASS
7.6.14. For how long did s/he have a mass in the abdomen? [00 = less than 1 day; 88 = not known; 99 = NA, no mass].....					MASSL
7.6.15. Was there a period of a day or longer when s/he did not pass any stools? .		1. Yes	2. No	8. NK	CONSTIP
7.6.16. During the illness that led to death, did he/she vomit everything?.....		1. Yes	2. No	8. NK	IVOMIT
7.6.17.1. How many days after birth did the baby start to vomit? [000 = less than 1 day; 888 = not known; 999 = NA, no vomiting].....					WHOVOMIT

7.6.17.2. When the vomiting was most severe, how many times did the baby vomit in a day? [000 = less than 1 day; 88 = not known; 99 = NA, no vomiting].....					WHOVDAY
7.6.18. Did s/he vomit "coffee grounds" or bright red / blood?.....	1. Yes	2 No	8. NK		VOMBLOOD

7.7 Injury

7.7.1. Did NAME die from an injury, accident, poisoning, bite, burn, or drowning that led to his / her death?.....	1. Yes	2. No	8. NK		INJURY1

IF THE INFANT DID NOT SUSTAIN AN INJURY THAT LED TO HER DEATH, DRAW A DOUBLE LINE THROUGH QUESTIONS 7.7.1.1 TO 7.7.15 AND MOVE STRAIGHT TO SECTION 7.8 OTHER PROBLEMS.

7.7.1.1. Was the injury or accident intentionally inflicted by someone else?.....	1. Yes	2 No	8. NK	9. NA	INTENTINJ
7.7.2. Was it a road traffic accident?.....	1. Yes	2 No	8. NK	9.NA	RTA

IF NO DRAW A DOUBLE LINE THROUGH Q7.7.2.1 TO Q7.7.2.6.8 AND CONTINUE WITH Q7.7.3.

If yes:

7.7.2.1. Was she injured as an occupant in a vehicle (car)?.....	1. Yes	2 No	8. NK	9.NA	CAR
7.7.2.2 Was she injured as an occupant in a bus or heavy transport?.....	1. Yes	2 No	8. NK	9.NA	BUS
7.7.2.3. Was she on a motorcycle?.....	1. Yes	2 No	8. NK	9.NA	MOTO
7.7.2.4. Was she on a pedal cycle?.....	1. Yes	2 No	8. NK	9.NA	BIKE
7.7.2.5. Was she being carried by a pedestrian?.....	1. Yes	2 No	8. NK	9.NA	PED
7.7.2.6. Do you know anything about the other vehicle / person hit in the road traffic	1. Yes	2 No	8. NK	9.NA	OTHVEH
If yes, did the accident involve:					
7.7.2.6.1. A pedestrian?.....	1. Yes	2 No	8. NK	9.NA	OTHPED
7.7.2.6.2. A stationary object?.....	1. Yes	2 No	8. NK	9.NA	OTHSTAT
7.7.2.6.3. A car?.....	1. Yes	2 No	8. NK	9.NA	OTHCAR
7.7.2.6.4. A bus or heavy transport vehicle?.....	1. Yes	2 No	8. NK	9.NA	OTHBUS
7.7.2.6.5. A motorcycle?.....	1. Yes	2 No	8. NK	9.NA	OTHMOTO
7.7.2.6.6. A pedal cycle?.....	1. Yes	2 No	8. NK	9.NA	OTHBICY
7.7.2.6.7. Something else?	1. Yes	2 No	8. NK	9.NA	OTHELSE
7.7.2.6.8. If yes, specify.....					OTHELSE2
7.7.3. Was she injured in a non-road transport accident?.....	1. Yes	2 No	8. NK	9.NA	NONRTA
7.7.4. Did she fall?.....	1. Yes	2 No	8. NK	9.NA	FALL
7.7.5. Did she drown?.....	1. Yes	2 No	8. NK	9.NA	DROWN
7.7.6. Was she poisoned?.....	1. Yes	2 No	8. NK	9.NA	POISONED
7.7. 7. Did she die due to burns?.....	1. Yes	2 No	8. NK	9.NA	BURN
7.7.8. Was she subject to violence or an assault?.....	1. Yes	2 No	8. NK	9.NA	ASSAULT
7.7.8.1. Was she killed by a firearm / gun?.....	1. Yes	2 No	8. NK	9.NA	FIREARM
7.7.8.2. Was she killed by a sharp object like a knife?.....	1. Yes	2 No	8. NK	9.NA	STAB
7.7.8.3. Did she die as a result of some other assault or abuse?.....	1. Yes	2 No	8. NK	9.NA	OTHASSAULT
7.7.8.3.1. If yes, please specify.....					OTHASSAULT
7.7.9. Did she suffer any animal / insect bite that led to her death?.....	1. Yes	2 No	8. NK	9.NA	BITE

7.7.9.1. Did she die following a dog bite?.....	1. Yes	2 No	8. NK	9.NA	DOG
7.7.9.2. Did she die following a snake bite?.....	1. Yes	2 No	8. NK	9.NA	SNAKE
7.7.9.3. Did she die following an insect bite?.....	1. Yes	2 No	8. NK	9.NA	INSECT
7.7.9.4. Did she die following another animal bite or sting?.....	1. Yes	2 No	8. NK	9.NA	OTHBITE
7.7.9.4.1. If yes, please specify.....					OTHBITE2
7.7.10. Was s/he injured by a force of nature?.....	1. Yes	2 No	8. NK	9.NA	NATURE
7.7.11. Was s/he injured by machinery?.....	1. Yes	2 No	8. NK	9.NA	MACH
7.7.12. Was s/he struck by an animal or object?.....	1. Yes	2 No	8. NK	9.NA	ANIM
7.7.13. Did she suffer from some other injury?.....	1. Yes	2 No	8. NK	9.NA	OTHINJ
7.7.13.1. If yes, please specify.....					OTHINJ2

7.7.14. How long did NAME survive after the injury, poisoning, bite, burn or drowning?

1. Died within 24 hours	2. Died 1 day later or more	3. Died at the site of the accident	DURINJ
8. NK	9. NA no injury or accident		

7.7. 15. After the accident, did she receive medical care before she died?.....	1. Yes	2. No	8. NK	MDCARE

7.8. Other problems

7.8.1. During the illness that led to death, did he/she have a fever?…….	1. Yes	2. No	8. NK	IFEVER
7.8.1.1. Was the fever severe?…….....	1. Yes	2. No	8. NK	9. NA	FEVSEV
7.8.1.2. Was the fever continuous or on and off?….....	1. Yes	2. No	8. NK	9. NA	FEVINT
7.8.1.3. Did s/he have chills or rigors?……....	1. Yes	2. No	8. NK	9. NA	RIGOR
7.8.2. How old was NAME in days when the fever started? [000 = Just born or less than 1 day; 888 = not known; 999 = NA, no fever].....					FEVERDAY
7.8.3. How long did the fever last in days? (IN DAYS) [00 = less than 1 day; 88 = not known; 99 = NA, no fever].....					FEVERNUM
7.8.3.1. How long before death did this fever start?.....	1. On the same day of death	2, 1 – 3 days before death	4. 4 – 7 days before death		FEVSTART
	4. More than one week before death		8. NK	9. NA	
7.8.4. During the illness that led to death, did NAME become cold to touch?	1. Yes	2. No	8. NK	COLD
7.8.5. How old was NAME when he/she became become cold to touch? (IN DAYS) [000 = Just born or less than 1 day; 888 = not known; 999 = NA, did not feel cold].....				COLDDAY
7.8.6. For how many days did NAME feel cold? (IN DAYS) [00 = less than 1 day; 88 = not known; 99 = NA, did not feel cold].....				COLDNUM
7.8.7. During the illness that led to death, did NAME become lethargic after a period of normal activity?	1. Yes	2. No	8. NK	LETHARGY
7.8.8. During the illness that led to death, did NAME have jaundice?	1. Yes	2. No	8. NK	IJAUND
7.8.8.1. Did s/he have yellow palms or soles?	1. Yes	2. No	8. NK	JAUNDE
7.8.8.2. Did the baby have yellow discoloration of the eyes?	1. Yes	2. No	8. NK	JAUNDS
7.8.8.3. How many days after birth did the yellow discolouration of the eyes begin? [000 = less than 1 day; 888 = not known; 999 = NA, no jaundice]				JAUNDB
7.8.8.4. For how many days did the yellow discolouration of the eyes last? [00 = less than 1 day; 88 = not known; 99 = NA, no jaundice].....				JAUNDL
7.8.9. During the illness that led to death, did he/she have redness of and drainage of pus from the eyes?.....	1. Yes	2. No	8. NK	CONJUNCT
7.8.10. During the illness that led to death, did he/she bleed from anywhere?.....	1. Yes	2. No	8. NK	HDN

7.8.11. During the illness that led to death, did he/she have a sunken fontanelle?		1. Yes	2 No	8. NK	SUNKFONT
7.8.12. Did NAME have an ongoing chronic illness or was he/she sick before the accident or injury?.....	1. Yes	2. No	8. NK	9. NA	INJURY2
7.8.12.1. If yes, what was the illness? (Please refer to code list)..……					CHRILL

8. POSTNEONATAL DEATHS - ADDITIONAL QUESTIONS ABOUT THE FATAL ILLNESS

COMPLETE THIS SECTION FOR POSTNEONATAL DEATHS ONLY.
FOR NEONATAL DEATHS PUT A DOUBLE LINE THROUGH THIS SECTION AND GO TO SECTION 9.
FOR STILLBIRTHS PUT A DOUBLE LINE THROUGH SECTIONS 8-10 AND GO TO SECTION 11.

8.1. Nutrition

8.1.1. During the illness that led to death, did NAME become very thin?.....	1. Yes	2. No	8. NK	THIN
8.1.2. Did NAME have "marasmus" during the month before he/she died?.....	1. Yes	2. No	8. NK	MARASMUS
8.1.3. During the illness that led to death, did NAME have swollen legs or feet?.....	1. Yes	2. No	8. NK	SWELL
8.1.4. How long did the swelling last in days? (IN DAYS) [00= less than 1 day; 88 = not known; 99 = NA, no swelling].....				SWELLDAY
8.1.5. During the illness that led to death, did NAME have a swollen face? ..	1. Yes	2. No	8. NK	SFACE
8.1.6. During the illness that led to death, did NAME have swollen joints?	1. Yes	2. No	8. NK	SJOINTS
8.1.7. During the illness that led to death, did NAME have a swollen ankles?	1. Yes	2. No	8. NK	SANK
8.1.8. During the illness that led to death, did NAME have swelling of the whole body?	1. Yes	2. No	8. NK	SBODY
8.1.9. For how long did the swelling last? (IN DAYS) [00 = less than 1 day; 88= not known; 99 = NA, no swollen body].....				SLAST
8.1.10. During the illness that led to death, did NAME's skin flake off in patches?	1. Yes	2. No	8. NK	FLAKE
8.1.11. During the illness that led to death, did NAME's hair change in colour to a reddish (or yellowish) colour?	1. Yes	2. No	8. NK	COLOR
8.1.11.1. For how long did s/he have reddish/yellowish hair? [00 = less than 1 day; 88 = NK; 99 = NA, no hair change].....				COLORD
8.1.12. Did NAME have "kwashiorkor" during the month before he/she died?.....	1. Yes	2. No	8. NK	KWASHIOR
8.1.13. During the illness that led to death, did NAME have 'lack of blood' or 'pallor'?.....	1. Yes	2. No	8. NK	BABANAEM
8.1.14. During the illness that led to death, did NAME have pale palms?	1. Yes	2. No	8. NK	BABPALE
8.1.15. During the illness that led to death, did NAME have white nails?	1. Yes	2. No	8. NK	BABWNAIL
8.1.16. For how long did s/he look pale or have pale palms or white nails? [00=less than 1 day;88=not known;99=NA,none].....				BABANL

8.2 Breathing

8.2.1. During the illness that led to death, did he/she have noisy breathing?.....	1. Yes	2. No	8. NK	NOISE
8.2.2. During the illness that led to death, did he/she have stridor? [DEMONSTRATE]…..……	1. Yes	2. No	8. NK	STRIDOR
8.2.3. During the illness that led to death, did he/she have wheeze? [DEMONSTRATE]?.....	1. Yes	2. No	8. NK	WHEEZE

8.3 Neurological problems

8.3.1 During the illness that led to death, did NAME have a stiff neck?.....	1. Yes	2. No	8. NK	STIFFNECK
8.3.2. For how long did she have a stiff neck [00 = less than 1 day; 01 to 28; 88 = not known; 99 = NA].....				STIFFNECKDU
8.3.3. During the illness that led to death, did NAME stop being able to grasp?	1. Yes	2. No	8. NK	GRASP

8.3.4. How long before he/she died did NAME stop being able to grasp?

1. Less than 12 hours	2. 12 hours or more	8. NK	9. NA, did not start or stop grasping	STOPGRASP

8.3.5. Did s/he have a headache?	1. Yes	2. No	8. NK		HACHE
8.3.6. Was the headache severe?	1. Yes	2. No	8. NK	9. NA	HACHES
8.3.7. For how long did the headache last? [00 = less than 1 day; 88= not known; 99 = NA, no headache].....					HACHEL
8.3.8. Did s/he have paralysis of the lower limbs?	1. Yes	2. No	8. NK		POLIO

8.3.9. Did the paralysis start suddenly quickly within a single day or slowly over many days?

1. Suddenly	2. Over a single day	3. Slowly over many days	8. NK	9. NA	POLIOS

8.3.10. During the illness that led to death, did NAME stop responding to a voice?.....	1. Yes	2. No	8. NK	VOICE

8.3.11. How long before he/she died did NAME stop being able to respond to a voice?

1. Less than 12 hours	2. 12 hours or more	8. NK	9. NA, did not start or stop responding to voice	STOPVOICE

8.3.12. During the illness that led to death, did NAME stop being able to follow movements with his/her eyes?.....	1. Yes	2. No	8. NK	FOLLOW

8.3.13. How long before he/she died did NAME stop being able to follow movements with his/her eyes?

1. Less than 12 hours	2. 12 hours or more	8. NK	9. NA, did not start or stop following	STOPFOLLOW

8.4 Skin problems

8.4.1. During the month before he/she died, did NAME have a skin rash?	1. Yes	2. No	8. NK		RASH
8.4.2. Was the rash all over NAME's body?	1. Yes	2. No	8. NK	9. NA no rash	GENRASH
8.4.3. Was the rash on NAME's face?	1. Yes	2. No	8. NK	9. NA no rash	FACRASH
8.4.4. Was the rash on NAME's trunk?	1. Yes	2. No	8. NK	9. NA no rash	TRUNKRASH
8.4.5. Was the rash on NAME's arms and legs?.....	1. Yes	2. No	8. NK	9. NA no rash	ARMSRASH
8.4.6. How many days did the rash last? (IN DAYS) [00 = less than 1 day; 88 = not known; 99 = NA, no rash].....					RASHDAY

8.4.7. What did the rash look like?

1. Measles rash	2. Rash with clear fluid	3. Rash with pus	8. NK	9. NA no rash	RASHAPP

8.4.8. Did the rash have blisters containing clear fluid?	1. Yes	2. No	8. NK	9. NA no rash	BLISRASH
8.4.9. Did the skin crack/split or peel after the rash started?	1. Yes	2. No	8. NK	9. NA no rash	CRKRASH
8.4.10. Was this illness "measles"?.....	1. Yes	2. No	8. NK	9. NA no rash	MEASLES
8.4.11. Did s/he have red eyes?	1. Yes	2. No	8. NK	9. NA no rash	REDEYES
8.4.12. When the baby had diarrhea, did you give ORS?.....	1. Yes	2. No	8. NK	9. NA	ORT
8.4.13. During the illness that led to death, did NAME have lumps in the armpits?.....	1. Yes	2. No	8. NK		AXLYMPH
8.4.14. During the illness that led to death, did NAME have lumps in the groin?.....	1. Yes	2. No	8. NK		INGLYMPH
8.4.15. During the illness that led to death, did NAME have lumps in the neck?.....	1. Yes	2. No	8. NK		NECKLYMPH
8.4.16. During the illness that led to death, did NAME have lumps in any other place?.....	1. Yes	2. No	8. NK		OTHLYMPH
8.4.17. For how long did these lumps last? [00 = less than 1 day; 88= not known; 99 = NA, no lumps].....					LYMPHL
8.4.18. During the illness that led to death, did NAME have mouth sores or a whitish rash inside the mouth or on the tongue?	1. Yes	2. No	8. NK		CANDIDA
8.4.19. For how long did these mouth problems last? [000 = less than 1 day; 888= not known; 999 = NA, no mouth problems].....					CANDL

8.5 Abdominal problems

8.5.1. Did s/he have abdominal pain?	1. Yes	2. No	8. NK		APAIN
8.5.2. How long did the abdominal pain last ? (IN DAYS) [00 = less than 1 day; 88 = not known; 99 = NA, no swelling].....					APAINL
8.5.3. Was the abdominal pain severe?	1. Yes	2. No	8. NK	9. NA	APAINS

8.6 Other problems

8.6.1 Did the baby have any urine problems?	1. Yes	2. No	8. NK		URINE

8.6.2 How much urine did s/he pass?

1. Too much	2. Too little	3. No urine at all	8. NK		URINEP
8.6.3. Was there any change to the amount of urine s/he passed daily?.....	1. Yes	2. No	8. NK		URINECHANG
8.6.4. For how long did this urine change last? [00 = less than 1 day; 88= not known; 99 = NA, no urine change].....……					URINEL
8.6.5. Did the baby pass no urine at all?.....	1. Yes	2 No	8. NK		NOURINE
8.6.6. During the final illness did s/he ever pass blood in the urine?.....	1. Yes	2 No	8. NK		BLOODURINE
8.6.7. Did the child have sunken eyes at any time during the final illness?.....	1. Yes	2. No	8. NK		SUNK
8.6.8. For how long did the sunken eyes last? 00 = less than 1 day; 88= not known; 99 = NA, no sunken eyes].....					SUNKL
8.6.9. Did s/he have bleeding from the nose, mouth or anus?	1. Yes	2. No	8. NK		BLEED
8.6.10. During the illness that led to death, did he/she have malaria?	1. Yes	2. No	8. NK		IMALARIA

9. INFORMATION ABOUT CARESEEKING

COMPLETE THIS SECTION FOR NEONATAL AND POSTNEONATAL DEATHS ONLY.
FOR STILLBIRTHS PUT A DOUBLE LINE THROUGH THIS SECTION AND GO TO SECTION 10.

9.1. Was care sought outside the home while NAME had this illness/injury?.....	1. Yes	2. No	8. NK	CARESEE
9.2. Was care sought from a doctor, nurse, clinic or hospital for this illness/injury?.....	1. Yes	2. No	8. NK	APPCARE
9.3. Was a traditional healer consulted for this illness/injury? ……	1. Yes	2. No	8. NK	OTHCARE
9.4. Was a religious leader consulted for this illness/injury?.....	1. Yes	2. No	8. NK	RELICARE
9.5. Was a community-based practitioner consulted for this illness/injury?.....	1. Yes	2. No	8. NK	COMMCARE
9.6. Was a private physician or nurse consulted for this illness/injury?.....	1. Yes	2. No	8. NK	PPHYCARE
9.7. Trained birth attendant?.....	1. Yes	2. No	8. NK	CSK_TBA
9.8. Homeopath?.....	1. Yes	2. No	8. NK	CARESK_HMPH
9.9. Did you seek care at a pharmacy for this illness/injury?.....	1. Yes	2. No	8. NK	PHARMCARE
9.10. Did you seek care from a drug seller, store or market for this illness/injury?	1. Yes	2. No	8. NK	DRUGCARE
9.11. Did you seek care from a relative or friend for this illness/injury?	1. Yes	2. No	8. NK	RELFRCARE
9.12. Did you seek care from any clinic, health post or hospital for this illness? .	1. Yes	2. No	8. NK	FACCARE
9.12.1. How many times?				FACCARENO
9.12.2. PLEASE PROVIDE FACILITY CODE1 [99=NA].....				CODECARE1
9.12.3 PLEASE PROVIDE FACILITY CODE2 [99=NA].....				CODECARE2

9.12.4 PLEASE PROVIDE FACILITY CODE3 [99=NA].....				CODECARE3
9.12.2. PLEASE PROVIDE FACILITY CODE4 [99=NA].....				CODECARE4
9.12.3 PLEASE PROVIDE FACILITY CODE5 [99=NA].....				CODECARE5
9.12.4 PLEASE PROVIDE FACILITY CODE6 [99=NA].....				CODECARE6
9.13. Did you seek care from any other source for this illness/injury? If yes, specify:_____	1. Yes	2. No	8. NK	OTHERCARE
9.14. How many days after the illness was care sought?				DCARS
9.15. In the final days did you travel with NAME to a hospital or health facility?..	1. Yes	2 No	8. NK	TRAVELHOSP

9.16. What mode of transport did you use to go to the hospital?.....	1. Walking / Foot	2. Bicycle	3. Motorbike	4. Car
	3. Taxi	4. Bus / Tro-Tro	5. Other, SPECIFY:	TRANSP

9.17. Where or from whom did you first seek care [USE FACILITY CODE LIST; 88=NK; 99=NA].....				CARESEEK1
9.18 Where or from whom did you seek care for the second time? [USE FACILITY CODE LIST; 88=NK; 99=NA].....				CARESEEK2
9.19. Where or from whom did you seek care for the third time? [USE FACILITY CODE LIST; 88=NK; 99=NA].....				CARESEEK3
9.20. Was NAME admitted to sleep at least one night in a hospital, health centre or other health institution during their final illness/injury?.....	1. Yes	2. No	8. NK	PLACEADM
9.21Where was NAME admitted? [USE FACILITY CODE LIST; 99 = not admitted].....				IHOSP

9.22. Where did NAME die?

			PLACEDIED
1. Clinic/hospital	2. Private maternity home	3. At home	
4. On route to clinic/hospital	5. Other:		

9.23. IF THE ANSWER TO 8.18. IS 1 OR 2, STATE WHERE. [USE FACILITY CODE LIST; NA=99].....				ADDPLDIED
9.24. If the baby was discharged from hospital, what was their condition on discharge?.....	1. Well	2. Somewhat unwell	3. Very unwell	DISCHILL
9.25. Did a health care worker tell you the cause of death?.....	1. Yes	2. No	8. NK	9. NA HWCOD

9.26. What did the health worker say?

	HWSAY

9.27. Were there any problems during admission to the hospital or health facility?.....	1. Yes	2 No	8. NK	ADMPROB
9.28. Were there any problems with the way [NAME] was treated in the hospital or health facility?.....	1. Yes	2 No	8. NK	TREATPROB
9.29. Were there any problems getting medications or diagnostic tests in the hospital or health facility?.....	1. Yes	2 No	8. NK	MEDPROB
9.30. Does it take more than 2 hours to get to the nearest hospital or health facility from [Name's household]?.....	1. Yes	2 No	8. NK	DISTFAC
9.31. the final illness were there any doubts about whether medical care was needed?.....	1. Yes	2 No	8. NK	DOUBTS
9.32. Was traditional medicine used?.....	1. Yes	2 No	8. NK	TRADITIONMED
9.33. At the time of death, did you use a telephone or cellphone to call for help?.	1. Yes	2 No	8. NK	CALLHELP

9.34. Over the course of [NAME's] illness, did the total costs of care and treatment prohibit other household payments?.....	1. Yes	2 No	8. NK	PROHIBCOST

10: TREATMENT AND RECORDS

COMPLETE THIS SECTION FOR NEONATAL AND POSTNEONATAL DEATHS ONLY.
FOR STILLBIRTHS PUT A DOUBLE LINE THROUGH THIS SECTION AND GO TO SECTION 11.

10.1. Medicines

10.1.1. Did NAME receive any medical therapy during their illness?.....	1. Yes	2. No	8. NK	DRUGS

IF NO THEN PUT A DOUBLE LINE THROUGH THIS SECTION AND GO TO SECTION 10.2

Did NAME receive any of the following?

10.1.2. Antibiotics …….....……	1. Yes	2. No	8. NK	IANTIB
10.1.3. Aspirin…….....……	1. Yes	2. No	8. NK	IASPIRIN
10.1.4. Anti-malarial……..…….....……	1. Yes	2. No	8. NK	IANTIMAL

10.1.5. If possible, please specify the antimalarial drug received….....	1. Chloroquine	2. Fansidar	3. Quinine	ANTIMT
	4. Artesonate	5. Amodiaquine	8. NK	
	6. Artesonate-Amodiaquine		9. NA	
	7. Other, specify:			

10.1.6. Other known oral medicine.....	1. Yes	2. No	8. NK	ORALMK
10.1.7. Other unknown oral medicine.....	1. Yes	2. No	8. NK	ORALMUK
10.1.8. Antibiotic injection.....	1. Yes	2. No	8. NK	ABINJ
10.1.9. Other injection.....	1. Yes	2. No	8. NK	OTHINJ
10.1.10. ORS.....	1. Yes	2. No	8. NK	ORS
10.1.11. IV drip.....	1. Yes	2. No	8. NK	IVDRIP
10.1.12 Blood transfusion.....	1. Yes	2. No	8. NK	BLOODTRANS
10.1.13 Treatment / food through tube passed through nose.....	1. Yes	2. No	8. NK	NGT
10.1.14 Other, SPECIFY:_____	1. Yes	2. No	8. NK	OTHMED

10.2. Surgery

10.2.1. Did s/he have any operation for the illness?.....	1. Yes	2. No	8. NK	OPER
10.2.2. How long before death did s/he have the operation? [00 = less than 1 day; 88 = not known; 99 = NA, no operation].....				OPERL

10.2.3 On what part of the body was the operation?

1. Abdomen	2. Chest	3. Head	4. Other, specify:	8. NK	9. NA	OPERP

10.2.3. Did s/he have any other operation before death?.....	1. Yes	2. No	8. NK	SURGB4DEAT

10.3 Immunisations

10.3.1. Did the baby have a BCG immunisation? (BCG) [DEMONSTRATE WHERE THE IMMUNISATION IS INJECTED INTO TOP OF ARM].....	1. Yes	2. No	8. NK	BCG
10.3.2. Did the baby have a measles immunisation at 6-12 months of age? [DEMONSTRATE WHERE THE IMMUNISATION IS INJECTED INTO THE ARM].....	1. Yes	2. No	8. NK	MEASIMM

10.3.3. To your knowledge, did the baby receive all the vaccinations that they were due before they died?.....	1. Yes	2. No	8. NK	VACC

10.4 Health records

10.4.1. Are there health records available? .....……..	1. Yes	2 No	8. NK	IRECORD
10.4.2. Can I transcribe the health records?	1. Yes	2 No	9. NA/ No health records	ITRANSC

10.4.3What type of health records does the respondent have?

Child health record / weighing card.....	1. Yes	2. No	8. NK	HTYPE1
Mother's ANC card.....	1. Yes	2. No	8. NK	HYTPE2
Burial permit.....	1. Yes	2. No	8. NK	HYTPE3
Hospital prescription.....	1. Yes	2. No	8. NK	HYTPE4
Treatment card.....	1. Yes	2. No	8. NK	HYTPE5
Postmortem result.....	1. Yes	2. No	8. NK	HYTPE6
Hospital discharge card …….....	1. Yes	2. No	8. NK	HYTPE7
Laboratory results ……	1. Yes	2. No	8. NK	HYTPE8
Other documents, SPECIFY: _____	1. Yes	2. No	8. NK	HYTPE9

IF THERE ARE NO HEALTH RECORDS PUT A DOUBLE LINE THROUGH THIS SECTION AND SECTION 10.5 AND GO TO SECTION 10.6

10.4.4. TRANSCRIBE ALL THE ENTRIES WITHIN THE 12 MONTHS BEFORE THE CHILD DIED IF RESPONDENT ALLOWS YOU TO SEE THE RECORDS. INCLUDE ALL DATES.

MAKE SURE YOU INCLUDE ALL IMMUNISATIONS. WRITE THE DATE OF THE LAST MEDICAL NOTE IN SECTION 10.4.5.

IENTRY

_____
_____
_____
_____
_____
_____

10.4.5. RECORD THE DATE OF THE LAST MEDICAL NOTE [090909 = no note].....									IMEDNOTE

10.5. Infant weight

10.5.1. RECORD THE TWO MOST RECENT WEIGHTS OF THE INFANT IN KILOGRAMS

No date = 080808, No weight = 88.88

DO NOT INCLUDE BIRTHWEIGHT. BIRTHWEIGHT SHOULD BE INCLUDED IN SECTION 5.
THE EARLIER ONE SHOULD BE DATE 1 AND THE LATER ONE SHOULD BE DATE 2 E.G. DATE 1 = 10/01/03, DATE 2 = 10/02/03.

Date 1			DATE1
Weight 1	.		WEIGHT1
Date 2			DATE2
Weight 2	.		WEIGHT2

10.6. Death certificate

10.6.1. Was a death certificate issued?	1. Yes	2 No	8. NK	DEATHC

ASK TO SEE THE DEATH CERTIFICATE AND RECORD WHETHER YOU ARE ABLE TO SEE IT.

10.6.2. ABLE TO SEE DEATH CERTIFICATE? .....……	1. Yes	2. No	9. NA no certificate	VIEWDC

DRAW A LINE THROUGH THIS SECTION IF NO CERTIFICATE

10.6.3. RECORD THE IMMEDIATE CAUSE OF DEATH FROM THE CERTIFICATE

	IMMCOD

10.6.4.RECORD THE FIRST UNDERLYING CAUSE OF DEATH FROM THE CERTIFICATE

	UNDCOD1

10.6.5. RECORD THE SECOND UNDERLYING CAUSE OF DEATH FROM THE CERTIFICATE

	UNDCOD2

10.6.6. RECORD THE THIRD UNDERLYING CAUSE OF DEATH FROM THE CERTIFICATE

	UNDCOD3

10.6.7. RECORD THE CONTRIBUTING CAUSE(S) OF DEATH FROM THE CERTIFICATE

	CONTCOD

11. ALCOHOL AND TOBACCO USE

11.1. Did NAMES mother ever drink alcohol?……...…….	1. Yes	2. No	8 NK	ALCOHOL
11.2. Did his/her mother ever smoke tobacco (cigarette, cigar, pipe etc.)?.....	1. Yes	2. No	8 NK	TOBACCCO

12. HIV/AIDS AND TUBERCULOSIS

SAY "THE FINAL QUESTIONS ABOUT THE BABY'S DEATH ARE ABOUT HIV/AIDS AND TB"

12.1. Has the child's mother ever been tested for "HIV/AIDS"?.....		1. Yes	2. No	8. NK	HIVTEST
12.2. Was the "HIV/AIDS" test ever positive? [9= NA / no test].….	1. Yes	2. No	8. NK	9. NA	HIVPOS
12.3. Has the child's mother ever been told she had "AIDS" by a health worker?.....		1. Yes	2. No	8. NK	HIVHW
12.4. Has anyone in the family been diagnosed as having tuberculosis?		1. Yes	2. No	8. NK	FAMTB
12.5. Did they live in the same house as this infant?	1. Yes	2. No	8. NK	9. NA	HOUSETB

13. INTERVIEWER COMMENTS AND OBSERVATIONS
Please write any additional comments or observations that you may have in this space.

END OF INFANT VPM FORM. THANK RESPONDENT(S) AND CHECK YOUR FORM.
